Advances in Bioengineering Research and Applications, Volume 2

Biomechanics of Artificial Organs and Prostheses

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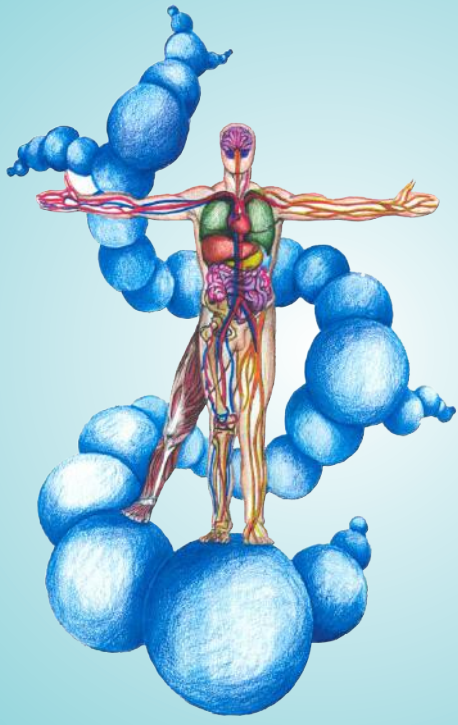
Vijay K. Goyal, PhD



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BIOMECHANICS OF ARTIFICIAL ORGANS AND PROSTHESES

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Megh R. Goyal, PhD, PE, and Vijay K. Goyal, PhD

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CONTENTS

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AIMBE	American Institute for Medical and Biological Engineering
ANNA	American Nephrology Nurses Association
ASABE	American Society of Agricultural and Biological Engineers
ASAIO	American Society for Artificial Internal Organs
ASAO	Austrian Society for Artificial Organs
ASB	American Society of Biomechanics
ASBMR	American Society of Bone and Mineral Research
ASME	American Society of Mechanical Engineers
BiVAD	Biventricular Assist Device
BMES	Biomedical Engineering Society
CHF	Congestive Heart Failure
CPB	Cardiopulmonary Bypass
CPS	Cardiopulmonary Support System
CVP	Central Venous Pressure
DT	Destination Therapy
ECG	Electrocardiogram
EDTA	European Dialysis and Transplantation Association
EMBS	Engineering in Medicine and Biology
ESAO	the European Society for Artificial Organs
ESB	European Society of Biomechanics
ESEM	European Society for Enginerring and Medicine
FDA	Food and Drug Administration, USA
HSTAT	Health Services Technology Assessment Texts
IABP	Intra Aortic Ballon Pump
IFAO	International Federation for Artificial Organs (formerly ISAO)
ISABB	International Society for Artificial Cells, Blood Substitutes & Biotechnology
ISAO	International Society for Artificial Organs
ISFA	International Society for Apheresis
ISPD	International Society for Peritoneal Dialysis
ISRP	International Society for Rotary Blood Pumps
JSAO	the Japanese Society for Artificial Organs
LVAD	Left Ventricular Assist Device
MedEc	Medical Economics
NCBI	National Center for Biotechnology Information
NIH	National Institute of Health, USA
NIHCBC	National Institute of Health Center for Biomedical Computation at Stanford University

NKF	National Kidney Foundation
ORS	Orthopaedic Research Society
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart
RMTES	Regenerative Medicine and Tissue Engineering Society
SMB	Society for Mathematical Biology
TAH	Total Artificial Heart
TERMIS	Tissue Engineering and Regenerative Medicine International
VAD	Ventricular Assist Device
VSD	Ventricular Septal Defect

PREFACE

I have been teaching fluid mechanics to undergraduate and graduate students since 1971. I decided to apply principles of fluid mechanics to human body systems: When my respiratory system collapsed in 1989 and I had three strokes in 2002 and my vagus nerve failed in 1999; my mother broke her hips and orthopedic surgeon did "Total Hip Replacement (THR)" and my mother survived 12 more years; my elder brother had a heart mitral valve replaced in 2003 and he feels perfectly fine; my mother-in-law passed away in 2010 with three heart valves damaged (she did not want to have a heart operation and she lived for next 4 years after diagnosis of heart disease); our neighbor in Puerto Rico had "Total Knee Replacement (TKR)" for both knees and now she can do her daily activities. I thought why would this happen to a human body, and I was able to understand that Almighty Supreme God grants serenity and knowledge to physicians so that we can live longer and happier. I also know a friend of mine with amputation of both legs and he does his daily activities using a wheel chair. All this fascinates my soul. Let us all keep our spirits high so that our life is always dynamic to be happier today/tomorrow and forever. This is how idea for this book was born.

Engineering mechanics deals with response of bodies at rest or in motion due to applied external forces/couples/torques/rotation/and moments. Biomechanics deals with living organisms: Agricultural plants, animals and humans. In this book, I will consider only human body systems. One is interested in variation of velocity, pressure, density, volume, momentum, heat, mass, nutrient or other parameter throughout the body. In the human body, I will consider only continuous bodies (i.e., there is no discontinuity at any point for a specific body part). Biomechanics and Computational Fluid Dynamics (CFD) is one of the specialty areas of biomedical engineering. Biomechanics applies classical mechanics (bodies at rest or in motion, thermodynamics, and continuum mechanics) to biological or medical problems. It includes the study of motion flow within our body and in medical devices, and transport of chemical constituents across biological and synthetic media and membranes. Progress in biomechanics has led to the development of the artificial organs and prostheses: Heart valves, stents, TKR, THR, etc.

Biomechanics is widely used in orthopedic industry to design orthopedic implants for human joints, dental parts, external fixations and other medical purposes. It also includes study of the performance and function of biomaterials used for orthopedic implants. It plays a vital role in improving the design and producing successful biomaterials for medical and clinical purposes.

The mission of this compendium is to serve as a textbook or a reference manual for graduate and undergraduate students of biomedical engineering, biotechnology, nanotechnology, nursing, and medicine and health sciences. I hope that it will be a valuable reference for professionals that work with medicine and health sciences, for nursing institutes, and other agencies that work with human health.

My book complements other similar books in the market and is unique because it is complete, simple, one-stop manual worldwide on *Biomechanics of Artificial Organs and Prostheses*. This textbook includes basic principles and applications of mechanics and materials for human body. This book is a must for physicians, scientists, educators, and students.

This book on *Biomechanics of Artificial Organs and Prostheses* consists of 12 chapters consisting of: Introduction on artificial organs; biofluid dynamics of cardiopulmonary bypass surgery; biomechanics of the artificial heart; biomaterials for an artificial pacemaker; biomechanics of the angioplasty: ballooning and stenting; biomechanics of carotid stenting; biomechanics of an artificial lung; biomechanics of the human kidney system and artificial kidney; biomechanics of the arthritis and human body pain; biomechanics of orthopedic fixations; biomechanics of total knee replacement; and biomechanics of dental prostheses. Each chapter includes an introduction, body of the chapter, conclusions, summary, key words and a bibliography. Book also includes a glossary of terms. This book is Volume 2 for the AAP series titled *Advances in Bioengineering Research and Applications*.

The chapters in this book are based on my research and teaching materials and special projects by my students in the courses on fluid mechanics/engineering mechanics/and mechanics of materials at University of Puerto Rico at Mayagüez and the course on biofluid mechanics at Florida International University. The contribution by my students at University of Puerto Rico at Mayagüez and Florida International University has been most valuable in the compilation of this compendium. Their names are mentioned in each chapter. In July of 2001, students of my course (INGE4015) in Fluid Mechanics conducted the first congress on "*Biofluid Dynamics of Human Body Systems*." The purpose of this congress was to show and learn how the biofluids of the many body systems function and help to maintain a great physical state. In this congress, student groups discussed Biofluid Dynamics of: Brain system; Ear/throat/nose system; Circulatory system; Reproductive system; Digestive system; Respiratory system; Urinary system; Arthritis; Instrumentation and measurements for the human body; Challenges in Biofluid dynamics of human body systems. In July of 2002, students conducted second congress on "*Biofluid Dynamics and Engineering of Artificial Organs*." The purpose of this congress was to learn biofluid dynamics of Bioheat Transfer in a Human Body, Biomass Transfer in a Human Body, Biofluid Mechanics of Artificial heart, Biofluid Mechanics of Artificial lung, and Biofluid Mechanics of Artificial kidneys. In April of 2003, students of my course on – BME4999 Human Body Systems – conducted third congress on "*Biofluid Dynamics of Human Body Systems*" to discuss: Circulatory System; Artificial Heart; Cardiovascular Bypass Surgery; Respiratory System; Kinetics of Drug Transport; Digestive System; Maternal Fetal System; Stenting of Intracranial Arteries as Endovascular Bypass of Berry Aneurysms (Baruch Barry Lieber, PhD, PE, University of Miami). In July of 2004, we conducted fourth congress on Biofluid Dynamics of Human Body Systems to discuss: Our Body Fluids; Properties of body fluids; Ear/nose and throat system; Balloning and stenting; Urinary system; Artificial kidney; Advances in human body fluids; dimensional analysis; Biomass transfer; Body pain; Instrumentation and measurements. It has been an excellent learning experience for me. I thank all of them at University of

Puerto Rico at Mayagüez and at Florida International University who have enriched my knowledge in Biomedical Engineering.

This book would not have been written without the valuable cooperation of a group of engineers and physicians at the University of Puerto Rico at Mayagüez (UPRM) and Florida International University (FIU). I am grateful to my colleagues: Paul Sundaram, Ricky Valentin, Carlos Rinaldi, David Suleiman, Madeline Torres, Eduardo Juan, Alejandro Acevedo, and Ivette Ríos Lamberty. Dr. Vijay K. Goyal, an associate professor of the Department of Mechanical Engineering at the University of Puerto Rico at Mayagüez with over 17 years of experience in advanced computational methods applied to structures, joins me as coauthor for this volume. He has been exploring and researching this field for a couple of years as he tried to develop a toolkit to predict bone regeneration. His insights and collaboration was invaluable for this volume. The reader will not have this edition in front of you without his offer without his professional contribution.

I owe special gratitude to Anthony McGoron at FIU and Richard Schoephoerster, now Dean of the College of Engineering at the University of Texas at El Paso – Texas, who taught me to love biomedical engineering during my sabbatical leave in 2003 at FIU. I had the opportunity to work closely with all of them including other faculty members. The author also thanks executive officers at UPRM Campus to initiate research in biomedical engineering and nanotechnology.

I would like to thank Ashish Kumar, Publisher and President, and Sandra Jones Sickels, VP, at Apple Academic Press, Inc., for making every effort to publish the book when the human health is a major issue worldwide. Special thanks are due to AAP Production Staff for typesetting the entire manuscript and for the quality production of this book.

I request the reader to offer me your constructive suggestions that may help to improve the next edition. The reader can order the copy of this book for the library, the institute or gift from www.appleacademicpress.com.

Finally, a river of thanks flows from my heart and soul to my wife Subhadra for the understanding and collaboration of sharing the responsibility, time and devotion necessary to prepare this book. With my whole heart and best affection, I dedicate this book to our youngest son Vinay Goyal and his wife Stacey Carpenter. They always motivate me to live longer and happier to serve the world community. I also dedicate this book to "*those who want to live happily*" by making personal health as first priority. One should not hesitate to discuss any personal health issues with a physician who are dedicated and blessed by Almighty Supreme God to do the maximum for alleviating our body pain. Good health not only makes us happy but also makes happy everyone around us.

— Megh R. Goyal, PhD, PE

December 31st 2013

FOREWORD

In 1994, Dr. Megh R. Goyal taught me courses on soil and water management and farm machinery when I was an undergraduate student at the University of Puerto Rico – Mayaguez Campus. He was one of my favorite professors. After receiving my BSc degree in agriculture sciences, I decided to enter the medical school to become a specialist in internal medicine and respiratory mechanics. After reading and editing this manuscript, I feel honored to write a foreword for this book, thus paying tributes to my professor.

I want to share with the readers what I learnt from textbooks on medical physiology by Arthur Guyton and other authors. The human body is a fascinating job of our Almighty God. It is made up of a head, neck, torso, two arms and two legs. The human body is made to stand erect, walk on two feet, use the arms to carry and lift, and has opposable thumbs (able to grasp). The adult body is made up of 100 trillion cells, 206 bones, 600 muscles, and 22 internal organs. Every square inch of the human body has about 19 million skin cells. Every hour about 1 billion cells in the human body must be replaced. The average human head has about 100,000 hairs. The arteries, veins and capillaries are about 100,000 kilometers long. The heart beats more than 2.5 billion times in an average lifetime. The human heart creates enough pressure to squirt the blood 30 feet high. It takes about 20 seconds for a red blood cell to circle the whole body.

The human body has nine major systems: circulatory system; respiratory system; musculoskeletal system; nervous system; reproductive system; digestive system; urinary system; lymphatic system; integumentary (dermal) system. Five minor systems are: immune system; excretory system; endocannabinoid system; endocrine system and vestibular (sensory) system. Each system plays a vital part in the health and well-being of the entire body.

The circulatory system pumps and channels blood to and from the body and lungs with heart, blood, and blood vessels. Blood is a medium that transports oxygen, from the respiratory system to the cells. Blood also transports sugars, chemicals, proteins, hormones and many other substances around the body for use and elimination. As the heart pumps blood, a pulse beat can be felt at various locations in the body and each pulse beat corresponds to one heartbeat. The heart rate of the average adult at rest is between 80 to 120 beats per minute, depending on age, medical conditions and general fitness.

The respiratory system is composed of the airway (mouth, nose, trachea, larynx, bronchi and bronchioles) and the lungs (including the small air sacs called alveoli). The respiratory system provides oxygen to the blood and takes away the waste product called carbon dioxide. Oxygen is extracted from air inhaled through the airway and goes into the blood stream through the membranes of the lungs. For the first aider, maintaining a casualty's airway is of primary importance.

The musculoskeletal system is composed of muscles that provide movement and a skeleton that provides structural support and protection with bones, cartilage, ligaments, and tendons. Most muscles used for movement work by contracting and relaxing in conjunction with a bone.

The digestive system helps in digestion and processing of food with salivary glands, esophagus, stomach, liver, gallbladder, pancreas, small and large intestines, rectum, and anus. Fluid and solids are passed through the esophagus to the stomach where they are processed for further digestion. They are then absorbed into the body through the membranes of the intestines. Some organs, such as the liver and pancreas, are considered accessories to the digestive system as they help process food into various chemical substances used by the body.

The urinary system (kidneys, ureters, bladder and urethra) is involved in fluid balance, electrolyte balance and excretion of urine. This system flushes waste products suspended in fluid from the body. It plays a vital role in keeping the body healthy. Should the urinary system fail (especially the kidneys), then the affected person requires external assistance to get rid of the waste products by 'flushing' the blood. This is called hemodialysis or dialysis.

The integumentary (dermal) system is composed of skin, hair and nails. The skin is the body's largest organ and plays an important role in protecting the body from infections. The other functions of skin include acting as a shield against injury and keeping body fluids in. The skin is made from tough, elastic fibers, which have the ability to stretch without tearing easily.

As a physician and a specialist in internal medicine and pulmonary mechanics, I work closely with my colleagues namely: cardiologist Marcos A Velazquez; dentist Luis Camacho; foot surgeon Andres Maymi; gastroenterologist Carlos Micames; gynecologist Walter Banch; hand surgeon Oscar Vargas; maxi-facial surgeon Juan C. Garcia; nephrologist Justiniano Alfredo; orthopedic surgeons Hector Vargas/Gilberto Baez/Jose Cancio; surgeon Juan A. Diaz; urologist Benjamin Perez; and including others. I see them with a smiling face and joy every time each one of them comes out of an operating room. We all are here to extend the best treatment in the market to our patients so that they feel happy and do not feel the body pain.

In this textbook, Professor Goyal applies principles of biomechanics and biomaterials to artificial organs and prostheses. He has wisely discussed all the topics with an abundance of illustrations and technical data. In the world of medicine, one of the greatest advancements has been the ability to create artificial organs and prostheses that can restore the proper function of a patient's body. They can be used both for functions that are essential to the quality of life of a patient. The organs that can be replaced artificially are quite numerous, including the ears, ovaries, and even the heart and brain. I will discuss only one example to emphasize the importance of engineering of artificial organs.

The most common manifestation of an artificial organ is found with mechanical aids that are used to improve a person's ability to hear and distinguish sounds. Called cochlear implants, the organs have been successful with nearly 200,000 people across the globe. In addition to improving the sense of hearing in those patients with impaired ears, the artificial organs are also able to provide a limited hearing ability to people

who are deaf. As this device becomes less expensive and more available, it is thought that the worldwide incidence of deafness will decrease dramatically. One case of a survival situation where an artificial organ will make the difference between life and death is in a heart transplant. If a patient is awaiting a new heart, an artificial heart can be temporarily used to keep the person alive until the new heart becomes available. In recent times, models have been created that can stand alone and provide a permanent replacement for a heart that has functional impairment. This new type of artificial heart is currently in the process of being evaluated and it is thought that it will be ready for widespread live use beginning in the year 2013. The availability of artificial organs can do much to improve a person's life, from providing the essential bodily functions for survival to improving sensory capabilities, such as sight and hearing.

I hope that this concise textbook by Dr. Megh R. Goyal and Apple Academic Press Inc. will be definitely appealing and valuable to the health sciences community. It is unique, user-friendly and introductory, focusing on essential aspects of *Biomechanics of Artificial Organs and Prostheses*. I will like to see more books on such topics.

Jesús Manuel Román Vélez, MD
Practicing Specialist in Internal Medicine, Pulmonary Mechanics
Fellow-American Society of Internal Medicine
Mayaguez, PR, USA

WARNING/DISCLAIMER

READ CAREFULLY

This textbook guides the world community on *Biomechanics of Artificial Organs and Prostheses* for better health. The reader must be aware that the dedication, commitment, honesty, and sincerity are most important factors in a dynamic manner for a complete success. It is not a one-time reading of this manual. Read and follow every time; it is needed. To err is human. However, we must do our best. Always, there is a space for learning new experiences.

The editor, the contributing authors, the publisher and the printing company have made every effort to make this book as complete and as accurate as possible. However, there still may be grammatical errors or mistakes in the content or typography. Therefore, the contents in this book should be considered as a general guide and not a complete solution to address any specific situation in the human body. For example, all humans are not same and behave differently.

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BOOK REVIEWS

"I am enthusiastic to know that Apple Academic Press Inc. and Dr. Megh R. Goyal (whom have I known since 1979) have published this textbook that is user-friendly and easy-to-read. The book includes key aspects of *Biomechanics of Artificial Organs and Prostheses*."

— Miguel A. Muñoz Muñoz, PhD, President of University of Puerto Rico, USA

"I hope that this concise textbook on artificial organs and prostheses by Dr. Goyal and Apple Academic Press Inc. will be definitely appealing and valuable to the health sciences community. It is unique and introductory focusing on essential aspects of *Biomechanics of Artificial Organs and Prostheses*. I will like to see more books on such topics."

— Jesús Manuel Román Vélez, M.D., Practicing Physician, Specialist in Internal Medicine and Pulmonary Mechanics, Fellow of American Society of Pulmonary Medicine, Mayaguez, PR, USA.

"What a gem, with simple language and vivid illustrations! The photos and data deepened my understanding on biomechanics and biomaterials of artificial organs and prostheses the way it applies to our daily life. Before I sat down to read this book, I was not sure how much I would understand the content. But each chapter builds understanding on the content and shows the author's mastery on the subject. I firmly believe that this book is a must read for all with interest in bioengineering and readers who want to make their health as their first priority."

— Prof. Raj Bansal, New Jersey, USA

ABOUT THE BOOK SERIES: ADVANCES IN BIOENGINEERING RESEARCH AND APPLICATIONS

Apple Academic Press, Inc. (AAP) is publishing volume 2, titled ***Biomechanics of Artificial Organs and Prostheses*** as part our AAP series titled ***Advances in Bioengineering Research and Applications.*** Previously, we have published volume 1, titled ***Biofluid Dynamics of Human Body Systems***. Volume 3, titled, ***Dictionary of Technical Terms: Bioengineering and Biotechnology*** is coming in 2014. Over a span of 8 to 10 years, Apple Academic Press, Inc. will publish subsequent volumes in the specialty areas defined by Biomedical Engineering Society (BMES). The mission of this series is to provide knowledge and techniques for biomedical and biological engineers. The series aims to offer academic researchers, scientists, university faculty, and students high-quality reference and academic content in bioengineering that is accessible to university-level students and professionals around the world. We thank BMES for granting the permission to use the following copyright material from <www.bmes.org/aws/bmes/pt/sp/be_faqs>. It has been edited/modified and reproduced below:

WHAT IS BIOMEDICAL ENGINEERING/BIOENGINEERING (BME)?

Pacela's *Bioengineering Education Directory* (Quest Publishing Co., 1990) has defined biomedical engineering, bioengineering, and clinical (or medical) engineering. According to Pacela, the scope of bioengineering is broader. Bioengineering is usually a basic research – oriented closely related to biotechnology/bionanotechnology and genetic engineering with a mission to improve agriculture plants or animals cells or human body cells. **BME** is the application of engineering principles and design concepts to medicine and biology. This field seeks to close the gap between engineering and medicine: It combines the design and problem-solving skills of engineering with medical and biological sciences to improve healthcare diagnosis, monitoring, and therapy. BME is, therefore, an interdisciplinary branch of engineering that ranges from theoretical, nontheoretical knowledge to state-of-the-art application in medicine and human health.

SPECIALTY AREAS OF BME

BME has only recently emerged as its own discipline, compared to many other engineering fields. Much of the work in BME consists of academics, research, and development. Prominent BME applications include the development of biocompatible prostheses, various diagnostic and therapeutic medical devices ranging from clinical equipment to microimplants, common imaging equipment such as MRIs

and EEGs, regenerative tissue growth, and pharmaceutical and therapeutic drugs. In BME there is continual change and creation of new areas due to rapid advancement in technology. However, some of the well-established specialty areas of BME are: bioelectricity; bioheat transfer; bioinformatics; bioinstrumentation; biomass transport; biomaterials; biomechanics; biotechnology/bionanotechnology; biosensors; cellular, tissue, genetic engineering, and transport phenomena; clinical engineering; medical imaging; orthopedic surgery; physiologic modeling; prosthetic devices and artificial organs; rehabilitation engineering; and systems physiology. These specialty areas frequently depend on each other. BMES has been the lead society to define some of these areas as below:

Bioinstrumentation is the application of electronics and measurement techniques to develop devices used in diagnosis and treatment of disease. Computers are an essential part of bioinstrumentation, from the microprocessor in a single-purpose instrument used to do a variety of small tasks to the microcomputer needed to process the large amount of information in a medical imaging system.

Biomaterials include both living tissue and artificial materials used for implantation. Understanding the properties and behavior of living material is vital in the design of implant materials. The selection of an appropriate material to place in the human body may be one of the most difficult tasks faced by the biomedical engineer. Certain metal alloys, ceramics, polymers, and composites have been used as implantable materials. Biomaterials must be nontoxic, noncarcinogenic, chemically inert, stable, and mechanically strong enough to withstand the repeated forces of a lifetime. Newer biomaterials even incorporate living cells in order to provide a true biological and mechanical match for the living tissue.

Biomechanics applies classical mechanics (statics, dynamics, fluids, solids, thermodynamics, and continuum mechanics) to biological or medical problems. It includes the study of motion, material deformation, flow within the body and in devices, and transport of chemical constituents across biological and synthetic media and membranes. Progress in biomechanics has led to the development of the artificial heart and heart valves, artificial joint replacements, as well as a better understanding of the function of the heart and lung, blood vessels and capillaries, and bone, cartilage, intervertebral discs, ligaments and tendons of the musculoskeletal systems.

Cellular, tissue and genetic engineering involve more recent attempts to solve biomedical problems at the microscopic level. These areas use the anatomy, biochemistry, and mechanics of cellular and subcellular structures in order to understand disease processes and to be able to intervene at very specific sites. With these capabilities, miniature devices deliver compounds that can stimulate or inhibit cellular processes at precise target locations to promote healing or inhibit disease formation and progression.

Clinical engineering is the application of technology to health care in hospitals. The clinical engineer is a member of the health care team along with physicians, nurses and other hospital staff. Clinical engineers are responsible for developing and maintaining computer databases of medical instrumentation and equipment records and for the purchase and use of sophisticated medical instruments. They may also work with physicians to adapt instrumentation to the specific needs of the physician

and the hospital. This often involves the interface of instruments with computer systems and customized software for instrument control and data acquisition and analysis. Clinical engineers are involved with the application of the latest technology to health care.

Medical imaging combines knowledge of a unique physical phenomenon (sound, radiation, magnetism, etc.) with high-speed electronic data processing, analysis and display to generate an image. Often, these images can be obtained with minimal or completely noninvasive procedures, making them less painful and more readily repeatable than invasive techniques.

Orthopaedic bioengineering is the specialty where methods of engineering and computational mechanics have been applied for the understanding of the function of bones, joints and muscles, and for the design of artificial joint replacements. Orthopaedic bioengineers analyze the friction, lubrication and wear characteristics of natural and artificial joints; they perform stress analysis of the musculoskeletal system; and they develop artificial biomaterials (biologic and synthetic) for replacement of bones, cartilages, ligaments, tendons, meniscus and intervertebral discs. They often perform gait and motion analyzes for sports performance and patient outcome following surgical procedures. Orthopaedic bioengineers also pursue fundamental studies on cellular function, and mechano-signal transduction.

Rehabilitation engineering is a growing specialty area of BME. Rehabilitation engineers enhance the capabilities and improve the quality of life for individuals with physical and cognitive impairments. They are involved in prosthetics, the development of home, workplace and transportation modifications and the design of assistive technology that enhance seating and positioning, mobility, and communication. Rehabilitation engineers are also developing hardware and software computer adaptations and cognitive aids to assist people with cognitive difficulties.

Systems physiology is a term used to describe that aspect of BME in which engineering strategies, techniques and tools are used to gain a comprehensive and integrated understanding of the function of living organisms ranging from bacteria to humans. Computer modeling is used in the analysis of experimental data and in formulating mathematical descriptions of physiological events. In research, predictor models are used in designing new experiments to refine our knowledge. Living systems have highly regulated feedback control systems that can be examined with state-of-the-art techniques. Examples are the biochemistry of metabolism and the control of limb movements.

Biotechnology, nanotechnology and bionanotechnology are sometimes used interchangeably with BME in general. **Biotechnology** is the use of biological processes, organisms, or systems to manufacture products intended to improve the quality of human life. The *United Nations Convention on Biological Diversity* defines biotechnology as any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. **Nanotechnology** is a study and use of structures between 1 nanometer and 100 nanometers in size. For example a width of a human hair is equivalent to eight hundred 100-nano-

meter particles side by side. Nanotechnology is the engineering of functional systems at the molecular scale. **Bionanotechnology or nanobiotechnology or nanobiology** is the harnessing of biological processes on an ultra-small scale in the manufacture and alteration of materials and products.

The presnt era is already preparing the foundation for **femtotechnology** and **bio-femtotechnology** during 22nd centrury.

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Volume 1: Biofluid Dynamics of Human Body Systems
Megh R. Goyal, PhD, PE

Volume 2: Biomechanics of Artificial Organs and Prostheses
Megh R. Goyal, PhD, PE, and Vijay K. Goyal, PhD

Volume 3: Dictionary of Technical Terms: Biotechnology and Bioengineering
Megh R. Goyal, PhD, PE

ABOUT THE AUTHOR

Dr. Megh R. Goyal received BSc degree in Engineering in 1971; MSc degree in 1977 and PhD degree in 1979; and Master of Divinity degree in 2001. He spent a one-year sabbatical leave in 2002–03 at the Biomedical Engineering Department, Florida International University, Miami – USA. He is a registered professional engineer in Puerto Rico and in India. Since 1971, he has worked as a Lecturer/Research Assistant at the Haryana Agricultural University and the Ohio State University; and Professor-cum-Research Agricultural and Biological Engineer at University of Puerto Rico – Mayaguez.

At present, he is a Retired Professor in Agricultural and Biomedical Engineering in the College of Engineering at University of Puerto Rico. He is also Senior Acquisitions Editor for Apple Academic Press, Inc., in the areas of agricultural science and biomedical engineering, as well as Senior Editor-in-Chief of the book series, Advances in Bioengineering Research and Applications, published by AAP.

He has authored more than 200 articles in technical journals and textbooks on *Elements of Agroclimatology* (Spanish) by UNISARC, Colombia; two *Bibliographies on Drip Irrigation*; *Biofluid Dynamics of Human Body*, *Management of Drip/Trickle or Micro Irrigation*, *Evapotranspiration: Principles and Applications for Water Management*, three-volume set on Research Advances on Sustainable Micro Irrigation, and Biomechanics of Artificial Organs and Prostheses, by Apple Academic Press Inc. Readers may contact him at: goyalmegh@gmail.com

ABOUT THE AUTHOR

Dr. Vijay K. Goyal received a BS in Mechanical Engineering from the University of Puerto Rico at Mayaguez and a PhD in Aeropsace Engineering from Virginia Tech. He is an associate professor at the University of Puerto Rico at Mayaguez with over 17 years of experience in advanced computational methods applied to structures. He has published over 25 technical publications, is the main author of two books (*Aircraft Structures for Engineers* and *Finite Element Analysis,* to be published by Pearson Education Publishers), and has been the recipient of several research grants from Lockheed Martin Co., ONR, and Pratt and Whitney.

He has extensively studied the static and dynamic failure response of composites using deterministic and stochastic approaches. His research is focused on dynamic stability of composite materials using nonlinear finite element methods, crack propagation of rotary composite blades, impact dynamics of composites, bird-strike modeling, behavior and simulations of micro/macro scale structures, fracture and fatigue of composites, fluid structure interaction to simulate wave propagation, and health monitoring of gears and bearings. Currently, he has been developing bone and tissue regeneration computational models. The main goal is to develop a computational model that will assist doctors to predict, based on scientific principles, whether the bone will regenerate or not and healing time for various treatments. This on-the-spot simulation with inputs from bone and blood samples would revolutionize how doctors treat broken bones. Readers may contact him at: vijay.goyal.dr@gmail.com

CHAPTER 1

INTRODUCTION

CONTENTS

The textbook on, ***Biomechanics of Artificial Organs and Prostheses***, is a Volume 2 for the AAP series titled: *Advances in Bioengineering Reasearch and Applications*, by Apple Acadmic Press Inc., In this volume, I will discuss in detail topics namely: Biofluid dynamics of cardio pulmonary bypass surgery; biomechanics of the artificial heart; biomaterials for an artificial pacemaker; biomechanics of the angioplasty: ballooning and stenting; biomechanics of carotid stenting; biomechanics of an artificial lung; biomechanics of the human kidney system and artificial kidney; biomechanics of the arthritis and human body pain; biomechanics of orthopedic fixations; biomechanics of total knee replacement; and biomechanics of dental prostheses. Most of the technical terms in each chapter are defined in the glossary at the end of this volume. In this chapter, we shall describe briefly the topics that are related to the "*Biomechanics of Artificial Organs and Prostheses*." Also the timeline for the development of artificial organs and prostheses describes the historical background, thus acknowledging exceptional contributions by scientists and educationists. List of biomechanics socities and journals is also presented.

1.1 BIOMECHANICS

Biomechanics (Ancient Greek: βίος «life» and μηχανική «mechanics;" Modern Greek, εμβιομηχανική) is the study of the structure and function of biological systems such as humans, animals, plants, organs, and cells by means of the methods of mechanics. In this book, we shall discuss only biomechanics of human body systems. The word biomechanics was developed in the 1970s, while describing the application of engineering mechanics to biological and medical systems.

Engineering biomechanics uses traditional engineering sciences to analyze biological systems. Applied mechanics, most notably mechanical engineering disciplines such as continuum mechanics, mechanism analysis, structural analysis, kinematics and dynamics play prominent roles in the study of biomechanics. Usually biological systems are more complex than man-built systems. Numerical methods are hence applied in almost every biomechanical study. Research is done in an iterative process of hypothesis and verification, including several steps of modeling, computer simulation and experimental measurements. Applied subfields of biomechanics include: Soft body dynamics, Kinesiology (kinetics + physiology), Animal locomotion and Gait analysis, Musculoskeletal and orthopedic biomechanics, Cardiovascular biomechanics, Ergonomy, Human factors engineering and occupational biomechanics, Implant (medicine)/Orthotics/Prosthesis, Rehabilitation, Sports biomechanics, and Allometry.

S**ports biomechanics** applies the laws of mechanics to gain a greater understanding of athletic performance and to reduce sport injuries as well. Elements of mechanical engineering (e.g., strain gauges), electrical engineering (e.g., digital filtering), computer science (e.g., numerical methods), gait analysis (e.g., force platforms), and clinical neurophysiology (e.g., surface EMG) are common methods used in sports biomechanics. Biomechanics in sports, can be stated as the muscular, joint and skeletal actions of the body during the execution of a given task, skill and/or technique. Proper understanding of biomechanics relating to sports skill has the greatest implications on: sport's performance, rehabilitation and injury prevention, along with sport mastery.

Continuum biomechanics is used for the mechanical analysis of biomaterials and biofluids. This assumption breaks down when the length scales of interest approach the order of the micro structural details of the material. One of the most remarkable characteristics of biomaterials is their hierarchical structure. In other words, the mechanical characteristics of these materials rely on physical phenomena occurring in multiple levels, from the molecular all the way up to the tissue and organ levels.

Biofluid mechanics is a study of body fluids that are at rest or in motion. Flow of body fluids can be modeled by the Navier–Stokes equations.

Biotribology is a study of friction, wear and lubrication of biological systems especially human joints such as hips and knees. For example, the principles of biotribology can determine the wear performance of the implant and lubrication effects of synovial fluid. In addition, the theory of contact mechanics helps in the wear analysis.

Comparative biomechanics is the application of biomechanics to nonhuman organisms. For example animal locomotion, has many manifestations: Running, jumping and flying. Locomotion requires energy to overcome friction, drag, inertia, and gravity, though which factor predominates varies with environment. Comparative biomechanics is often applied in medicine (with regards to common model organisms such as mice and rats) as well as in biomimetics, which looks to nature for solutions to engineering problems.

Plant biomechanics is the application of biomechanical principles to crops and plant organs.

The study of biomechanics ranges from the inner workings of a cell to the movement and development of limbs, to the mechanical properties of soft tissue, and bones. Biomechanics is also applied to study human musculoskeletal systems.

Biomechanics is widely used in orthopedic industry to design orthopedic implants for human joints, dental parts, external fixations and other medical purposes. It also includes study of the performance and function of biomaterials used for orthopedic implants. It plays a vital role to improve the design and produce successful biomaterials for medical and clinical purposes. For in depth study, the reader is advised to study following books (list may not be complete):

- Anthony C. Fischer-Cripps, *Introduction to Contact Mechanics*, ISBN 0-387-68187-6.
- Donald R. Peterson and Joseph D. Bronzino. *Biomechanics: Principles and Applications*, ISBN 0-8493-8534-2.
- Jagan N. Mazmudar. *Biofluid Mechanics*, ISBN 981-02-0927-4.
- Jay D. Humphrey. *Cardiovascular Solid Mechanics*, ISBN 0-387-95168-7.
- Lee Waite and Jerry Fine. *Applied Biofluid Mechanics*, ISBN 0-07-147217-7.
- Megh R Goyal, 2013. Biofluid *Dynamics of Human Body Systems*. Apple Academic Press Inc., ISBN: 9781926895468.
- Munson, Bruce R., Alric P. Rothmayer, Theodore H. Okiishi, and Wade W. Huebsch. *Fundamentals of Fluid Mechanics*. 7th Edition, 2013. John Wiley & Sons.
- Stephen C. Cowin. *Bone Mechanics Handbook*, ISBN 0-8493-9117-2.
- Temenoff, J. S. and Antonios G. Mikos, 2008. *Biomaterials: The Intersection of Biology and Materials Science*, ISBN 978-0-13-009710-1.

- Y.C. Fung. *Biomechanics*, ISBN 0-387-94384-6.
- Young, D. F., B. R. Munson, T. H. Okiishi and W. W. Huebsch. *A Brief Introduction to Fluid Mechanics*. 5th Edition, 2011. John Wiley.

1.2 HISTORY OF BIOMECHANICS

<http://www.asbweb.org/html/biomechanics/genealogy/genealogy.htm>
R. Bruce Martin, Ph.D., ASB Founding Member and President (1998–1999) described the history of biomechanics at the annual conference of the American Society of Biomechanics at University of Pittsburgh, Pittsburgh, PA, USA. The conference was held on October 23, 1999 <http://www.asbweb.org/html/biomechanics/genealogy/genealogy.htm>. Interest in biomechanics is ancient. From its earliest manifestations, science has looked inward as well as outward. This involved questions of epistemology but also human physiology, including biomechanics. The interest in biomechanics springs from the same source as Aristotle's – curiosity about the human body. The difference is that modern scientific activities are specialized in biomechanics, while Aristotle's interest was only part of a much wider pursuit of science. Edited and expanded version of speech by Martin is presented below:

470 B.C. Socrates was born on 470 B.C. in Athens – Greece. He believed that philosophy should achieve practical results for the greater well being of society. He attempted to establish an ethical system based on human reason rather than theological doctrine. He pointed out that human choice was motivated by the desire for happiness. Ultimate wisdom comes from knowing oneself. The more a person knows, the greater his or her ability to reason and make choices that will bring true happiness. He taught that we could not begin to understand the world around us until we understood our own nature.

424 B.C. Ancient Greek philosopher Plato (born in 424 B.C. in Athens, Greece) was the student of Socrates and the teacher of Aristotle. After Socrates' death, Plato traveled for 12 years throughout the Mediterranean region. He studied mathematics with the Pythagoreans in Italy and geometry, geology, astronomy and religion in Egypt. His conceptualization of mathematics as the life force of science created the necessary womb for the birth and growth of mechanics.

384 B.C. Ancient Greek philosopher Aristotle was born circa 384 B.C. in Stagira, Greece. Aristotle had a remarkable talent for observation and was fascinated by anatomy and structure of living things. Indeed, Aristotle might be considered the first biomechanician. He wrote the first book called "*De Motu Animalium*" – On the Movement of Animals. He not only saw animals' bodies as mechanical systems, but pursued such questions as the physiological difference between imagining performing an action and actually doing it.

130 AD Galen was born on 130 AD at Pergamon – Asia Minor. With the fall of Greece and the rise of the Roman Empire, natural philosophy waned in favor of technology. In Smyrna (now Izmir, Turkey), he wrote his first treatise: *On the Movements of the Heart and Lung.*

161–192 AD Galen, anatomist and physician, completed his major works, *On the Usefulness of the Parts of the Body* (in 17 books: meaning the parts of the human body) and *On the Natural Faculties,* as well as many other treatises. For the next 15 centuries, no other biomechanician was seen.

1452 AD Leonardo da Vinci was born on April 15, 1452, in Vinci – Italy. As an engineer and artist, he made substantial contributions to mechanics in the course of pursuing his numerous military and civil engineering projects and imaginative inventions, ranging from water skis to hang gliders. He had an understanding of components of force vectors, friction coefficients, and the acceleration of falling objects, and had a glimmering of Newton's Third Law. By studying anatomy in the context of mechanics, da Vinci also gained some insight into biomechanics. He analyzed muscle forces as acting along lines connecting origins and insertions and studied joint function. His drawings of a fetus in utero, the heart and vascular system, sex organs, and other bone and muscular structures, are some of the first on human record. One of his last commissioned works was a mechanical lion that could walk and open its chest to reveal a bouquet of lilies.

1514 Andreas Vesalius was born on Dec. 31, 1514, in Brussels. In 1539, he wrote an essay on *bloodletting* in which he described the veins that draw blood from the side of the torso. This led to the discovery of the circulation of blood by William Harvey. In 1543, he published in Basel *De humani corporis fabrica libri septem* (Seven Books on the Construction of the Human Body): Book 1 on the bones was generally correct but represented no major advance. Book 2 on the muscles was a masterpiece. Book 3 on blood vessels was exactly the opposite. Somewhat better was book 4 on the nerves, a great advance on everything written on the topic before, but it was largely outmoded a century later. Excellent was his treatment in book 5 on the abdominal organs. Book 6 dealt with the chest and neck, while book 7 was on the brain.

1514 Copernicus introduced the concept of a heliocentric solar system in 1514. *On the Revolutions of the Heavenly Spheres* not only revolutionized astronomy, it revolutionized science by reintroducing mathematical reasoning, the antithesis of Aristotelian common-sense physics. This had direct implications for biomechanics, too, because the desire to explain the orbits of the heavenly spheres led directly to the development of mechanics.

1564 Galileo Galilei was born on February 15, 1564 in Pisa in the Duchy of Florence – Italy. In 1604 at Padua, Galileo published *The Operations of the Geometrical and Military Compass*, revealing his skills with experiments and practical technological applications. He also constructed a hydrostatic balance for measuring small objects. These developments brought him additional income and more recognition. That same year, Galileo refined his theories on motion and falling objects, and developed the universal law of acceleration, which all objects in the universe obeyed. Galileo began to express openly his support of the Copernican theory that the earth and planets revolved around the sun. In 1612, he published his *Discourse on Bodies in Water*, refuting the Aristotelian explanation of why objects float in water, saying that it wasn't because of their flat shape, but instead the weight of the object in relation to the water it displaced. In 1632, Galileo defended his views in *Dialogue Concerning the Two*

Chief World Systems. Galileo's contribution to our understanding of the universe was significant not only in his discoveries, but in the methods he developed and the use of mathematics to prove them. He played a major role in the scientific revolution and deserves the moniker of "The Father of Modern Science." The father of mechanics and biomechanician, Galileo made important contributions to biomechanics. He was particularly aware of the mechanical aspects of bone structure and the basic principles of allometry. For example, he noted that:

- Mass of an animal increases disproportionately to the size, and the bones must consequently also disproportionately increase in girth, adapting to loadbearing rather than mere size.
- She bending strength of a tubular structure: Bone is increased relative to its weight by making it hollow and increasing its diameter.
- A marine animal can be larger than a terrestrial animal because the water's buoyancy relieves the weight of tissues.

Allometry is the study of the relationship of body size to shape, anatomy, physiology and finally behavior, first outlined by Otto Snell in 1892, D'Arcy Thompson in 1917 and Julian Huxley in 1932. Allometry is a well-known study of shape analysis for theoretical developments and applications to the differential growth rates of the parts of a body of a living organism. One application is in the study of various insect species (e.g., the Hercules Beetle), where a small change in overall body size can lead to an enormous and disproportionate increase in the dimensions of appendages such as legs, antennae, or horns. The relationship between the two measured quantities is often expressed as a power law or a logarithmic law (Equations (1) and (2)):

$$Y = k*(x^a) \tag{1}$$

or

$$\text{Log } Y = a*(\text{Log } x) + (\text{Log } k) \tag{2}$$

Where: a is a scaling exponent of the logarithmic law. Methods for estimating this exponent from data use type 2 regressions such as major axis regression or reduced major axis regression as these account for the variation in both variables, contrary to least squares regression, which does not account for error variance in the independent variable (e.g., log body mass). Other methods include measurement error models and a particular kind of principal component analysis. Allometry often studies shape differences in terms of ratios of the objects' dimensions. Two objects of different size but common shape will have their dimensions in the same ratio. Take, for example, a biological object that grows as it matures. Its size changes with age but the shapes are similar. Studies of ontogenetic allometry often use lizards or snakes as model organisms because they lack parental care after birth or hatching and because they exhibit a large range of body size between the juvenile and adult stage. Lizards often exhibit allometric changes during their ontogeny.

1608 Giovanni Borelli was born on 28 January 1608 in the district of Castel Nuovo, in Naples. Borelli believed that the planets were revolving as a result of three forces: The first force involved the planets' desire to approach the sun; the second

force dictated that the planets were propelled to the side by impulses from sunlight, which is corporeal; and the third force impelled the planets outward due to the sun's revolution. The result of these forces is similar to a stone's orbit when tied on a string. Borelli's measurements of the orbits of satellites of Jupiter are mentioned in Volume 3 of Newton's Principia. Trained in mathematics, Borelli also made extensive studies of Jupiter's moons, the mechanics of animal locomotion and, in microscopy, of the constituents of blood. He also used microscopy to investigate the stomatal movement of plants, and undertook studies in medicine and geology. Borelli is considered to be the first man to consider a self-contained underwater breathing apparatus along with his early submarine design. Borelli's major scientific achievements are focused around his investigation into biomechanics. This work originated with his studies of animals.

Borelli's publications, *De Motu Animalium I* and *De Motu Animalium II,* relate animals to machines and use mathematics to prove his theories (*See* Fig. 1). Borelli suggested that 'muscles do not exercise vital movement otherwise than by contracting'. He was also the first to deny corpuscular influence on the movements of muscles. This was proven through his scientific experiments demonstrating that living muscle

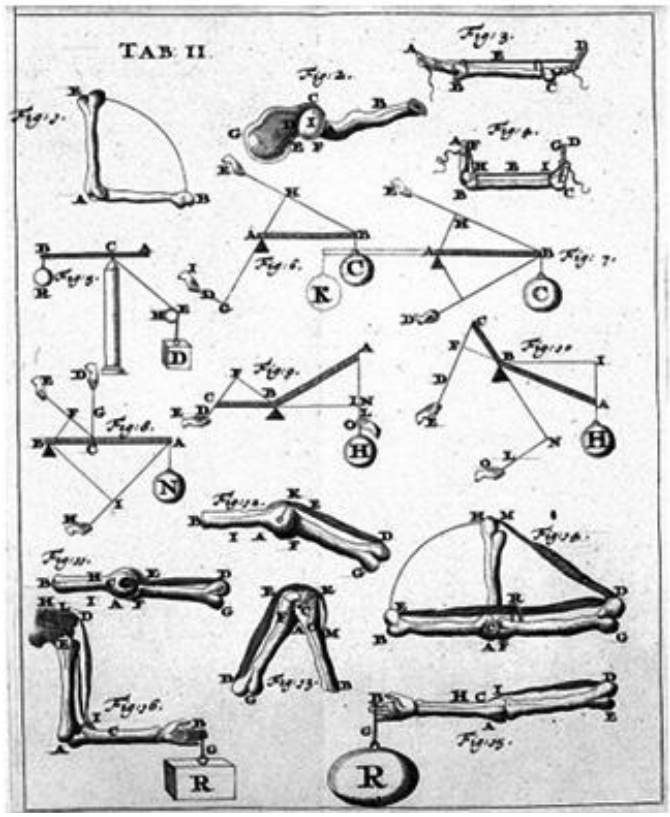


FIGURE 1 A sample page from the first works of Biomechanics (De Motu Animalium) by Giovanni Alfonso Borelli (Father of biomechanics): January 1st of 1680.

did not release corpuscles into water when cut. Borelli also recognized that forward motion entailed movement of a body's center of gravity forward, which was then followed by the swinging of its limbs in order to maintain balance. His studies also extended beyond muscle and locomotion. He imagined that the action of the heart was similar that of a piston. He derived the idea that the arteries have to be elastic. Borelli Figured out the forces required for equilibrium in various joints of the human body well before Newton published the laws of motion. He also determined the position of the human center of gravity, calculated and measured inspired and expired air volumes, and showed that inspiration is muscle-driven and expiration is due to tissue elasticity. For these discoveries, **Borelli is labeled as the father of modern** biomechanics and the American Society of Biomechanics uses the Borelli Award as its highest honor for research in the area.

1658 Marcello Malpighi was first of the greatest of the early microscopists, and the father of embryology. He, Borelli, and Descartes were key Figures in establishing the iatrophysical approach to medicine (Denoting a school of medical thought in the 17th century that explained all physiologic and pathologic phenomena by the laws of physics) They indicated that mechanics rather than chemistry was the key to understanding the functioning of the human body.

1850 After Borelli, there is little sign of biomechanics in the literature until the latter half of the 19th century, which Benno Nigg has called "the gait century." The idea of investigating locomotion using cinematography may have been suggested by the French astronomer Janssen; but it was first used scientifically by Etienne Marey, who first correlated ground reaction forces with movement and pioneered modern motion analysis. In Germany, the Weber brothers hypothesized a great deal about human gait, but it was Christian Wilhelm Braune and his student Otto Fischer who significantly advanced the science using recent advances in engineering mechanics. During the same period, the engineering mechanics of materials began to flourish in France and Germany under the demands of the industrial revolution. Engineers had learned about principal stresses from Augustine Cauchy, and German engineers were actually calculating the stresses in railroad bridges when they designed them – a novel idea for cut and try American and English engineers! This led to the rebirth of bone biomechanics when the railroad engineer Karl Culmann and the anatomist Hermann von Meyer compared the stress patterns in a human femur with those in a similarly shaped crane. Then Julius Wolff heard about their conversation, and **Wolff's Law** of bone remodeling was described that has been foundation of orthopedic medicine/mechanics in twentieth century.

1974 Herbert Hatze defined *"Biomechanics is the study of the structure and function of biological systems by means of the methods of mechanics."*

1977 The American Society of Biomechanics (ASB) was founded in October 1977 by a group of 53 scientists and clinicians.

1999 What is the future of biomechanics, the American Society of Biomechanics (ASB), and science in general? Will competition for resources among the increasing

population of scientists fractionate science even more? The modern model for success has been to find a niche – a subspecialized research topic – and stay within it. At the 1999 annual meeting of ASB, R. Bruce Martin indicated that "*biomechanics should represent the broad interplay between the two, including the subdisciplines defined in our bylaws, and more*."

20th century Yuan-Cheng Fung, a member of the United States National Academy of Sciences, has been known as the "father of modern biomechanics" for pioneering the application of quantitative and analytical engineering principles to the study of the human body and disease.

2004 A National Institutes of Health Center for Biomedical Computation at Stanford University was established with a mandate to provide leading software and computational tools for physics-based modeling and simulation of biological structures (<http://nmbl.stanford.edu/>). OpenSim, a free software, was designed to propel biomechanics research by providing a common framework for investigation and a vehicle for exchanging complex musculoskeletal models. Since then, this software (OpenSim) is being continuously developed by Simbios. **OpenSim** is an open source software system for biomechanical modeling, simulation and analysis. Its purpose is to provide free and widely accessible tools for conducting biomechanics research and motor control science. OpenSim enables a wide range of studies, including analysis of walking dynamics, studies of sports performance, simulations of surgical procedures, analysis of joint loads, design of medical devices, and animation of human and animal movement. The software performs inverse dynamics analysis and forward dynamics simulations. OpenSim is used in hundreds of biomechanics laboratories around the world to study movement and has a community of software developers contributing new features. OpenSim 1.0 was released on August 20, 2007 and provided capabilities for viewing musculoskeletal models, importing models developed in SIMM (Musculographics Inc.), editing muscle paths, and generating muscle actuated simulations that track experimental data. OpenSim 1.1 was released on December 11, 2007, which added new features such as user-specified camera positions for recording movies of simulations, and a perturbation (sensitivity) analysis for inquiry into the function of individual muscles. OpenSim 2.2.1 was released on April 11, 2011. This software update enhanced the user interface and allowed the user to set bounds on activations of muscles and actuators relating to static optimization not dynamic optimization. OpenSim 2.4 was released on October 10, 2011. This newest and most recent update includes faster and more robust tools for Inverse Dynamics and Inverse Kinematics, new visualization tools, enhanced access for API users, and many usability improvements. More information can be found at following web-links:

<http://simtk.org/>, <http://simtk.org/home/opensim/>, <http://simbios.stanford.edu/> <http://opensim.stanford.edu/>

1. SCIENTIFIC JOURNALS IN BIOMECHANICS (List may not be complete)

- Applied Bionics and Biomechanics
- Biomechanics and Modeling in Mechanobiology
- Clinical Biomechanics
- Computer Methods in Biomechanics and Biomedical Engineering
- Footwear Science
- Gait and Posture
- Journal of Applied Biomechanics
- Journal of Applied Physiology
- Journal of Arthroplasty
- Journal of Biomechanical Engineering
- Journal of Biomechanics
- Journal of Bone and Joint Surgery
- Journal of Electromyography and Kinesiology
- Journal of Experimental Biology
- Journal of Experimental Zoology
- Journal of Morphology
- Sports Biomechanics
- The Journal of Experimental Biology

2. BIOMECHANICS AND BIOENGINEERING SOCIETIES

<http://www.asbweb.org/html/links/links.html>

American College of Sports Medicine

American Physiological Society

American Society of Biomechanics

American Society of Mechanical Engineers

Australian and New Zealand Society of Biomechanics

Biophysical Society

Canadian Society for Biomechanics

European Society of Biomechanics

Federation of American Societies for Experimental Biology

Gait and Clinical Movement Analysis Society

German Society of Biomechanics

Hellenic Society of Biomechanics

Human Factors and Ergonomics Society

Instituto de Biomecánica de Valencia

International Society of Biomechanics

International Society of Biomechanics in Sports

International Society of Electrophysiology and Kinesiology

Japanese Society of Biomechanics

Orthopaedic Research Society

Societe de Biomecanique

Society for Integrative and Comparative Biology

Society for Mathematical Biology

Taiwanese Society of Biomechanics

The American Society of Biomechanics

The American Society of Bone and Mineral Research

The Biomedical Engineering Society

The Orthopaedic Research Society

3 BIOMECHANICS AND BONE WEBSITES

- Biomechanics course materials, <uoregon.edu/~karduna>
- Biomechanics World Wide <per.ualberta.ca>
- Biomed experts http://www.biomedexperts.com/
- Boise State University—*Center for Orthopaedic and Biomechanics Research*
- Bone Net
- Boston University—*Orthopaedic and Developmental Biomechanics*
- Columbia University—*Bone Bioengineering*
- Columbia University—*Musculoskeletal Biomechanics*
- Cornell University
- Johns Hopkins
- Mayo Clinic—*Biomechanics and Motion Analysis*
- Michigan State University—*Orthopaedic Biomechanics*
- Milk Matters
- National Osteoporosis Foundation
- NIH National Resource Center for Osteoporosis and Bone Related Diseases
- NIOSH Musculoskeletal Disorder Program, <cdc.gov>
- Ohio State University—*Biodynamics*
- Oregon State University—*Biomechanics*
- Powerful Bones. Powerful Girls.
- Rice University—*Computational Biomechanics*
- The ASBMR bone curriculum
- U.S. Center for Disease Control, <cdc.gov>
- UC San Francisco *Orthopaedic Bioengineering*
- University of California Berkeley—*Orthopaedic Biomechanics Laboratory*
- University of Michigan—*Orthopaedic Research Laboratory*
- USC Engineering Neuroscience and Health Seminar series (<bbdl.usc.edu/enh>)
- Whitaker Foundation <whitaker.org>

1.3 INTRODUCTION TO ARTIFICIAL ORGANS

An artificial organ is a man-made device that is implanted or integrated into a human body to replace a natural organ, for the purpose of restoring a specific function or a group of related functions so the patient may return to as normal a life as possible. Reasons to construct and install an artificial organ, an extremely expensive process initially, which may entail many years of ongoing maintenance services not needed by a natural organ, might include:

- Life support to prevent imminent death while awaiting a transplant (e.g. artificial heart).
- Dramatic improvement of the patient's ability for self-care (e.g. artificial limb).
- Improvement of the patient's ability to interact socially (e.g. cochlear implant).
- Cosmetic restoration after cancer surgery or accident.

Dr Eleni V. Antoniadou, Head of the Biosciences Department at Transplants Without Donors LLC, mentioned in her talk at the 2012 Annual Meeting of the Regenerative Medicine and Tissue Engineering Society the following: "*From a humanistic standpoint, the major aim of creating artificial organs is to give an end to the human organ trafficking, a transnational organized crime, that is rising in third world countries and has become a lucrative facet of economic development by annihilating the need for real organs*."

The replaced function does not necessarily have to be related to life support. The device must not be continuously tethered to a stationary power supply, or other station-

ary resources, such as filters or chemical processing units. Periodic rapid recharging of batteries, refilling of chemicals, and/or cleaning/replacing of filters, would exclude a device from being called an artificial organ. Thus a dialysis machine, while a very successful and critically important life support device that completely replaces the functions of a kidney, is not an artificial organ. At this time an efficient, self-contained artificial kidney has not yet become available.

In medicine, **one of the greatest advancements has been the ability to create artificial organs that are able to restore the proper function of a patient's body.** They can be used both for functions that are essential to life and also for purposes that are not related to survival but do improve a person's quality of life. The organs that can be replaced artificially are quite numerous, including the ears, ovaries, and even the heart and brain. Perhaps the most common manifestation of an artificial organ is found with mechanical aids that are used to improve a person's ability to hear and distinguish sounds. The cochlear implants have been successful with nearly 200,000 people across the globe. In addition to improving the sense of hearing in those patients with impaired ears, the artificial organs are also able to provide a limited hearing ability to people who are deaf. One case of a survival situation where an artificial organ will make the difference between life and death is in a heart transplant. If a patient is awaiting a new heart, an artificial heart can be temporarily used to keep the person alive until the new heart becomes available. In recent times, models have been created that can stand-alone and provide a permanent replacement for a heart that has functional impairment. This new type of artificial heart is currently in the process of being evaluated and it is thought that it will be ready for widespread live use beginning in the year 2013. The availability of artificial organs can do much to improve a person's life, from providing the essential bodily functions for survival to improving sensory capabilities, such as sight and hearing.

1.3.1 EXAMPLES OF ARTIFICIAL ORGANS (LIST MAY NOT BE COMPLETE)

i. Another idea is implanting a "**Language Translator**" for diplomatic and military applications. While machine translation does exist, it is presently neither good nor small enough to fulfill its promise.
ii. **Artificial bladders** are autologous laboratory-grown living replacements, as opposed to most other artificial organs which depend upon electro-mechanical contrivances, and may or may not incorporate any living tissue.
iii. Artificial bone.
iv. Artificial heart.
v. **Artificial human ovary** has been developed at Brown University with self-assembled micro-tissues created using novel 3-D petri dish technology. The artificial ovary will be used for the purpose of in vitro maturation of immature oocytes and the development of a system to study the effect of environmental toxins on folliculogenesis.
vi. Artificial limbs: Artificial arms and legs.
vii. Artificial lungs.
viii. Artificial pacemaker.
ix. Artificial pancreas.

x. Artificial skin.
xi. Auditory brainstem implant.
xii. Beyond restoration: It is also possible to construct and install an artificial organ to give its possessor abilities, which are not naturally occurring. Research is proceeding, particularly in areas of vision, memory, and information processing, however this idea is still in its infancy. Some current research focuses on restoring inoperative short-term memory in accident victims and lost access to long-term memory in dementia patients.
xiii. Bioartificial liver device intended for the treatment of liver failure using stem cells.
xiv. Bionic contact lens.
xv. Brain pacemakers, including deep brain stimulators.
xvi. Cardia and pylorus valves
xvii. Cochlear implant.
xviii. Decellularization.
xix. Ocular prosthetic.
xx. One area of success was achieved in 2002 when a British Scientist, Kevin Warwick, had an array of **100 electrodes fired into his nervous system** in order to link his nervous system into the internet. With this in place he carried out a series of experiments including extending his nervous system over the internet to control a robotic hand, a form of extended sensory input and the first direct electronic communication between the nervous systems of two humans.
xxi. Retinal implant.
xxii. Surgeons in Sweden performed the first implantation of a synthetic trachea in July 2011. Stem cells taken from the patient's hip were treated with growth factors and incubated on a plastic replica of his natural trachea.
xxiii. Tissue scaffold.
xxiv. To treat erectile dysfunction, both corpora cavernosa can be irreversibly surgically replaced with **manually inflatable penile implants**.
xxv. Ventricular assist devices.
xxvi. Visual prosthesis.
xxvii. Visual prosthetic.
xxviii. Etc.

1.4 TIMELINE: HISTORY OF ARTIFICIAL ORGANS

1885 — M. von Frey and M. Gruber (Leipzig) built and used the first artificial heart-lung apparatus for organ perfusion studies. Their device relies on a thin film of blood and included heating and cooling chambers, manometers, and sampling outlets, which permits monitoring of temperature, pressure, and blood gases during perfusion.

1891 German surgeon Theophilus Gluck performed first knee surgery. He also experimented with a number of different materials, including harvested muscle and fat, nylon and pig bladders to cushion the knee joint and relieve pain. He is also believed

to have performed the first true knee replacement surgery, using ivory to simulate the knee joint structure. The ivory joint was hinged and stabilized using plaster or metal.

1891–1950s There was little improvement in knee replacement surgery from the late 19th century through the 1950s. Gluck's ivory and plaster technique was updated several times using metal and plastic components, but they were still formed into a hinge-type device that was both inflexible and prone to complication and failure.

1895 — C. Jacobj (Germany) described complex organ perfusion apparatus that relies on donor lungs for gas exchange.

1913 — J.J. Abel, L.C. Rowntree and B.B. Turner at Johns Hopkins Hospital, Baltimore first described in vivo hemodialysis of rabbits, dogs (and later a 400 ml blood exchange in a human) with an artificial kidney made of collodion and using hirudin anticoagulant.

1915 —N. Richards and C. Drinker (Philadelphia) reported use of a screen oxygenator for perfusion of isolated organs in which venous blood flows by gravity down a cloth in an oxygen-rich atmosphere.

1916 — The anticoagulant heparin was discovered by McLean and Howell.

1925 — G. Haas (Germany) performed first clinical hemodialysis of 5 patients, using a modification of the Hopkins artificial kidney.

1927 — H. Necheles in Beijing developed the first "sandwich" artificial kidney using a biological membrane consisting of calves' peritoneal membrane and dialyzes dogs.

1928 — H.H. Dale and E.H.J. Schuster (Hampstead, UK) described a double perfusion pump (for pulmonary and systemic circulations) relying on compressible diaphragms to circulate defibrinated blood during organ perfusion experiments. J. Gibbon, Jr. subsequently uses this type of pump for early laboratory development of heart-lung apparatus.

1929 — S. Brukhonenko and S. Tchetchuline (Russia) maintained temporary function of guillotined dogs' heads using donor lungs for gas exchange and a bellows-type pump for blood circulation.

1934 — M.E. DeBakey (New Orleans) described dual-roller pump for transfusion of blood. This device subsequently becomes the most widely used type of blood pump for clinical applications of cardiopulmonary bypass and hemodialysis.

1937 — V. Demikhov employed an extracorporeal assist device for 5.5 hours to substitute for the cardiac function of a dog.

1939 — W. Thalheimer (New York) performed the first hemodialysis of a dog using cellophane membrane and heparin anticoagulation.

1939 — Robert E. Gross of Boston performed the first successful ligation of a patent ductus arteriosis.

1940 — Heparin is used for the first time in human patients by Gordon Murray of Toronto.

1943 — W. Kolff (Kampen, The Netherlands) developed a rotating drum artificial kidney and later the Kolff-Brigham dialyzer (designed and constructed in Boston), which became the standard throughout the 1950s.

1945/6 — N. Alwall (Lund, Sweden) developed first stationary drum artificial kidney and the first artificial ultrafiltration kidney capable of negative pressure and hydrostatic ultrafiltration.

1945/6 — G. Murray (Toronto) developed a stationary drum artificial kidney.

1949 — The Skeggs-Leonards kidney, designed by L. Skeggs and J. Leonards, was the first practical flat-plate dialyzer and is used clinically in Cleveland, Ohio.

1951 — Dubost of Paris replaced the abdominally aorta an aortic homograph.

1952 — Kolff-Brigham artificial kidney was used by the U.S. Army in 11th field hospital in Korea under unit chief P. Teschan.

1952 — Arterial graphs made of cloth were first described by Voorhees and Blakemore.

1953 — J. Gibbon, Jr. (Philadelphia) performed first successful clinical use of the heart-lung machine for cardiac surgery (closure of atrial septal defect).

1954 — Intra-cardiac surgery was performed by C. Laughton Lillehei using cross circulation from a healthy donor.

1954 Leslie Gordon Percival Shiers, pioneer of knee replacement surgery, published his original papers in the Journal of Bone and Joint Surgery in 1954. Shiers refused to patent his invention, and demonstrated the procedure throughout the world, inviting other surgeons to improve upon his original idea.

1955 — First meeting of the American Society for Artificial Internal Organs was held at the Hotel Chelsea in Atlantic City, New Jersey with 67 founding members.

1955 — Landmark publication: Kolff WJ. The artificial kidney – past, present and future. Tr Am Soc Artif Intern Org 1:1–7

1955 — Landmark publication: Clowes GHA Jr, Hopkins AL, Kolobow T. Oxygen diffusion through plastic films. Tr Am Soc Artif Intern Org 1:23–24.

1955 — Landmark publication: Gibbon JH Jr. Artificial heart-lung machines: Chairman's address. Tr Am Soc Artif Intern Org 1:58–62.

1955 — W. Kolff and his research team (Cleveland) developed a disposable twin-coil dialyzer.

1950s — After the brief involvement of Allis-Chalmers and Westinghouse, the Baxter Corporation manufactured the first widely used commercial dialyzing machine – the Baxter/Travenol recirculating U-200 twin-coil dialyzer.

1955 — American Society of Artificial Internal Organs was organized (<www.asaio.com>, 7700 Congress Avenue Suite 3107 Boca Raton, Florida 33487–1356, Telephone: 561–999–8969, Fax: 561–999–8972, Email: <info@asaio.com>): **A Premier Society** that brings together the interests and talents of physicians, scientists, engineers, industry and entrepreneurs dedicated to the continually evolving field of artificial organs. Formed in 1955 to "promote the increase of knowledge about artificial internal organs and of their utilization," it was the forum for first presentations about devices replacing the function of kidneys, hearts, lungs, pancreas and other organs. Dr. L.W. Bluemle Jr. said, "I think we realized for the first time that we did have soul mates in an important field." The same is true today. In the words of Dr. Thomas Depner, "ASAIO is a way of thinking, an orientation, an attitude, or a state of mind that promotes scientific investigation and innovation for the good of people who need artificial internal organs." The peer reviewed ASAIO Journal, and close cooperation with societies in Europe and Japan, ASAIO provides unique opportunities for investigators interested in artificial organ development and also for young investigators to interact with established experts and sponsoring companies. Due largely to ASAIO and its members, artificial hearts, lungs, kidneys, blood vessels and joints are now in common practice and entire new fields of clinical medicine have emerged, including nephrology, cardiac and vascular surgery, transplantation and intensive care.

1956 — G. Clowes (Cleveland) developed first successful membrane oxygenator-by 1960s further laboratory research studying function and improvement of membrane lungs is undertaken by Kolobow, Peirce, Galletti, Bramson and Hill, Landé and Lillehei, Drinker and Bartlett.

1956 — Landmark publication: Clark LC Jr. Monitor and control of blood and tissue oxygenation. Tr Am Soc Artif Intern Org 2:41–45, 1956.

1957 — W.J. Kolff, T. Akutsu and their research team (Cleveland) successfully implanted a hydraulic, polyvinyl chloride total artificial heart in a dog, keeping the animal alive for 90 minutes.

1957 — DeWall-Lillehei helix reservoir disposable bubble oxygenator was developed at the University of Minnesota and used in a series of 250 patients, which makes cardiopulmonary bypass safe and reliable for other teams worldwide.

1957 — Landmark publication: Edwards W.S. and Tapp J.S.. Two and a half years experience with crimped nylon grafts. Tr Am Soc Artif Intern Org 3:70–77.

1958 — Landmark publication: Hufnagel C, Villegas A. Aortic valvular replacement. Tr Am Soc Artif Intern Org 4:235–239.

1960 — The Quinton-Scribner shunt, developed by W. Quinton and B. Scribner in Seattle, Washington, made chronic renal dialysis possible.

1960 — Landmark publication: Quinton W., Dillard D. and Scribner B.H. Cannulation of blood vessels for prolonged hemodialysis. Tr Am Soc Artif Intern Org 6:104–113.

1960 — Landmark publication: Scribner BH, Buri R, Caner JEZ, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: A preliminary report. Tr Am Soc Artif Intern Org 6:114–122.

1960 — R. Stewart developed first hollow fiber dialyzer.

1960 — First successful intracardiac prosthetic valve operation was conducted by Albert Starr of Portland, Oregon.

1960s — Following John Charnley's success with hip replacement in the 1960s, attempts were made to design knee replacements. Knee replacements with hinged implants were available. However, hinged implants did not allow to bend or rotate the knees. These would often come apart soon after surgery and had a high infection rate. Frank H. Gunston and Leonard Marmor were pioneers in North America. Marmor's design allowed for unicompartmental operations but did not always last well.

1962 — Japanese Society for Artificial Organs was established, <http://www.jsao.org/english/183.html>.

1962 — Cimino and Brescia developed the subcutaneous arterio-venous shunt for chronic hemodialysis.

1962 — The first successful kidney transplant in unrelated humans is performed by Joseph Murray of Boston.

1963 — Landmark publication: Kolobow T and Bowman RL. Construction and evaluation of an alveolar membrane heart lung. Tr Am Soc Artif Intern Org 9:238–245.

1963 — Landmark publication: Nosé Y, Mikami J, Kasai Y, Sasaki E, Agishi T, Danjo Y. An experimental artificial liver using extracorporeal metabolism with sliced or granulated canine liver. Tr Am Soc Artif Intern Org 9:358–362, 1963.

1963 — D. Liotta and C.W. Hall (Houston) fabricated a tubular left ventricular assist device (LVAD), which is implanted by S. Crawford and M.E. DeBakey, but the patient does not survive. The Smithsonian's National Museum of American History, Artificial Organ Collection has this LVAD, donated by Dr. Hall.

1964 — Established by the National Heart and Lung Institute, the U.S. Artificial Heart Program, led initially by F. Hasting and later C. Dennis and J. Watson, encouraged and supported further research and development of cardiac replacement devices (L. Harmison, P. Frommer and F. Altieri all serve important periods of time as Acting Chief for the Total Artificial Heart program).

1964 — Landmark publication: Gott VL, Whiffen JD, Koepke DE, Daggett RL, Boake WC, Young WP. Techniques of applying a graphite-benzalkonium-heparin coating to various plastics and metals. Tr Am Soc Artif Intern Org 10:213–217, 1964.

1964 — Proportioning pump dialysis machine with safety monitors developed in Seattle. First longterm unattended overnight dialysis with this machine begun in Seattle.

1966 — Landmark publication: Eschbach JW Jr, Wilson WE Jr, Peoples RW, Wakefield AW, Babb AL, Scribner BH. Unattended overnight home hemodialysis. Tr Am Soc Artif Intern Org 12:346–366.

1966 — Landmark publication: Chang ™. Semi-permeable aqueous micro capsules (artificial cells) with emphasis on experience in extracorporeal systems. Tr Am Soc Artif Intern Org 12:13–19.

1966 — A. Kantrowitz (New York) successfully implanted into a patient an aortic U-shaped auxiliary ventricle intended as destination therapy for congestive heart failure.

1966 — M.E. DeBakey (Houston) performed the first successful clinical implantation of a ventricular assist device (a pneumatically driven paracorporeal diaphragm pump) in a 37-year-old woman who cannot be weaned from cardiopulmonary bypass following aortic and mitral valve replacement. She was supported for 10 days and discharged in less than a month. The original pump implanted in this patient was made by D. Liotta with the help of engineers from Rice University. Later, this pump was improved, and it was called the BCM-Rice pump. A prototype pump is available at the International Center for Medical Technologies in Houston, Texas.

1967 — The first human cardiac transplant was carried out by Christian Barnard of South Africa.

1967 — The first clinical use of the capillary fiber kidney developed by R. Stewart, and thereafter was universally used for long-term hemodialysis.

1967 — The double-leaflet prosthetic cardiac valve was described by Lillehei and Kaster at ASAIO.

1967 — Landmark publication: Henderson LW, Besarb A, Michaels A, Bluemle Jr. Blood purification by ultrafiltration and fluid replacement (diafiltration). Tr Am Soc Artif Intern Org 13:216–225.

1967 — Landmark publication: Menno, AD, Zizzi J, Hodson J, McMahon J. An evaluation of the radial arterio-venous fistula as a substitute for the Quinton shunt in chronic hemodialysis. Tr Am Soc Artif Intern Org 13:62–76.

1967 — A. Kantrowitz demonstrated clinical effectiveness of the intraaortic balloon pump in cardiogenic shock patients, with its potential for treatment in acute heart failure.

1968 — The first successful human liver transplant was reported by Thomas Starzl of Denver.

1968 — A nuclear powered energy cell for implantable cardiac devices in animals was described by J. Norman at ASAIO.

1968 — Landmark publication: Kantrowitz A, Tjonneland S, Krakauer J, Butner AN, Phillips SJ, Yahr WZ, Sharpiro M, Freed PS, Jaron D, Sherman JS Jr. Clinical experience with cardiac assistance by means of intraaortic phase-shift balloon pumping. Tr Am Soc Artif Intern Org 14:344–348.

1968 — Landmark publication: Chardack WM, Gage AA, Greatbatch W. Experimental observations and clinical experiences with the correction of complete heart block by an implantable self-contained pacemaker. Tr Am Soc Artif Intern Org 7:286–295.

1969 — D.A. Cooley, in the first clinical application of the total artificial heart, implanted a pneumatically powered heart designed by D Liotta (from the laboratory of M.E. DeBakey) as a bridge-to-transplantation into a 47-year-old male who survives 64 hours on the TAH and 32 hours following transplantation.

1969 — Landmark publication: Cooley D, Liotta D, Hallman GL, Bloodwell RD, Leachman RD, Milam RC. First human implantation of cardiac prosthesis for staged total replacement of the heart. Tr Am Soc Artif Intern Org 15:252–263. (Discussion following: Kwan-Gett CS, Wu Y, Collan R, Jacobsen S, Kolff WJ. Total replacement artificial heart and driving system with inherent regulation of cardiac output. Tr Am Soc Artif Intern Org 15:245–251, 1969).

1970 — Landmark publication: Schuder JC, Stoeckle H, Gold JH, West JA, Keskar PY. Experimental ventricular defibrillation with an automatic and completely implanted system. Tr Am Soc Artif Intern Org 16:207–212.

Early 1970s In the 1970s the "Geometric" design, and John Insall's Condylar Knee design, found favor. Hinged knee replacements for salvage date back to GUEPAR but did not stand up to wear. The researchers at Massachusetts General Hospital developed a rounded plastic component that closely resembled the traditional knee structure and allowed for total joint replacement. Their design is often referred to as "total condylar knee." However, only two different sizes were available. The concept of replacing the tibiofemoral condylar surfaces with cemented fixation, along with preservation of the cruciate ligaments, was developed and refined. To correct severe knee deformities, the condylar knee with posterior cruciate-sacrificing design was also introduced. By 1974, replacing the patellofemoral joint and either preserving or sacrificing the cruciate ligaments became a standard practice.

1971 — A. Kantrowitz implanted the dynamic aortic patch (now called the Kantrowitz CardioVad) in a patient with terminal heart failure. This 63-year-old man is the first patient to be discharged to home with a cardiac assist device intended as destination therapy for congestive heart failure.

1972 — End-Stage Renal Disease (ESRD) Act was passed in the USA ensuring federal support for chronic kidney disease management.

1972 — J.D. Hill, T.G. O'Brien and others (San Francisco) reported first successful clinical case using extracorporeal membrane oxygenation (ECMO) for respiratory failure.

1974 — European Society for Artificial Organs was founded in Geneva, Switzerland to encourage and publish progress made in the field of artificial organs and allied spheres, <http://www.esao.org/general.php>.

1974 — Landmark publication: Dobell WH, Mladejovsky MG. The directions for future research on sensory prostheses. Tr Am Soc Artif Intern Org 20:425–429.

1974 — Lung Division of the National Heart and Lung Institute proposes a multicenter prospective randomized study of ECMO in adult respiratory failure; study begins in 1975.

1975 — Five different membrane oxygenators for ECMO were manufactured and used, including the Kolobow Sci-Med, the Landé-Edwards, the Peirce-GE, the Bramson, and the Kolobow «Teflo."

1975 — R.H. Bartlett, A.B. Gazzaniga and their colleagues (University of California, Irvine) reported first successful clinical case of neonatal ECMO ("Esperanza").

1975 — Landmark publication: Bartlett RH, Gazzaniga AB, Jeffries MR, Huxtable RF, Haiduc NJ and Fong SW. Extracorporeal membrane oxygenations (ECMO) cardiopulmonary support in infancy. Tr Am Soc Artif Intern Org 22:80–93.

1975 — The first NIH-sponsored multicenter clinical trial for temporary support in acute ventricular dysfunction (primarily postcardiotomy), using the model 7 and model 10 Axio-symmetric LVADs (Thermo Electron Corp) and Pierce-Donachy LVAD (Thoratec).

1976 — International Society for Artificial Cells, Blood Substitutes and Biotechnology (ISABB) was formed in 1976 to encourage research, development and clinical applications in artificial cells, blood substitutes, nanomedicine, regenerative medicine, tissue engineering, cell/stem cell therapy, hemoperfusion, bioencapsulation, and related areas. <http://www.medicine.mcgill.ca/artcell/ISABI.htm >

1976 — The United States Food and Drug Administration (FDA), established in 1931, began regulating medical devices with passage of the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act, which seeks to provide "reasonable assurance of safety and effectiveness" for all medical devices.

1977 — Landmark publication: Rohde TD, Blackshear PJ, Varco RL, Buchwald H.Protracted parenteral drug infusion in ambulatory subjects using an implantable infusion pump. Tr Am Soc Artif Intern Org 23: 13–16.

1977 — The Heart and Vascular Division of the National Heart and Lung Institute issued a request for proposals (RFP) for components of a totally implantable LVAD, and subsequently awards multiple contracts, establishing the current generation of pulsatile systems.

1977 — the International Society for Artificial Organs (ISAO) was founded. In 2003, it was decided to transition begin the transition effective January 1, 2004 from a Society based on individual members into the International Federation for Artificial Organs (IFAO). The IFAO is based on Societies as members, with 3 founding member societies: the American Society for Artificial Organs (ASAIO), the European Society for Artificial Organs (ESAO) and the Japanese Society for Artificial Organs (JSAO), <http://www.ifao.org/about/history/>. The mission of IFAO is to encourage knowledge and

research on artificial organs, apheresis, tissue engineering, regenerative medicine and other related topics, to facilitate the international exchange of knowledge, and to provide education related to the improvement and optimal utilization of organ assist devices.

1978 — Landmark publication: Portner PM, Oyer PE, Jassawalla JS, Miller PJ, Chen H, LaForge DH, Skytte KW. An implantable permanent left ventricular assist system for man. Tr Am Soc Artif Intern Org 24: 98–103.

1978 — Continuous ambulatory parenteral dialysis was reported by Oreopoulous at ASAIO.

1978 — BioMedicus Biopump disposable centrifugal pump (which was originally designed as an artificial heart by H. Kletschka) became commercially available as an alternative to the roller pump for cardiopulmonary bypass.

1979 — Continuous arterial venous hemofiltration was described by Kramer of Goettingen, Germany.

Late 1970s to early 1980s — The condylar knee designs were improved to include modularity and noncemented fixation, with use of universal instrumentation. The mobile-bearing knee replacement was designed and developed during the late 1970s and early 1980s at Martland Hospital – New Jersey by Fred Buechel, a surgeon, and Michael Pappas, an engineer. The Buechel-Pappas joint replacement system is still widely used today. It is still being perfected and updated. A mobile-bearing replacement allows the synthetic joint platform to rotate, as opposed to a fixed-bearing joint, which is more stationary.

1980 — Continous AV hemofiltration was used for acute renal failure by Paganini of Cleveland.

1981 — Landmark publication: Malchesky PS, Asanuma Y, Smith JW, Kayashima K, Zawicki I, Werynski A, Blumenstein M, Nosé Y. Macromolecule removal from blood. Tr Am Soc Artif Intern Org, 27:439–44.

1982 — W. DeVries (Salt Lake City) implanted the pneumatic Jarvik-7 version of the TAH developed by W. Kolff and co-workers at the University of Utah as a permanent cardiac replacement into patient Barney Clark who survives 112 days with the device.

1982 — Extracorporeal CO_2 removal was described by Kolobow.

1983 — Landmark publication: Joyce LD, DeVries WC, Hastings WL, Olsen DB, Jarvik RK, Kolff WJ. Response of the human body to the first permanent implant of the Jarvik-7 total artificial heart. Tr Am Soc Artif Intern Org, 29:81–87.

1984 — In the first successful clinical application of an electrically powered, implantable system, the Novacor LVAS was developed by P. Portner is implanted in patient Robert St. Laurent, representing the first successful bridge-to-transplantation.

1984 — The role of starvation and nutrition in mortality from acute renal failure was described by Mault at ASAIO.

1985 — Crossover year during which one-half of all cardiopulmonary bypass procedures in the USA were performed with disposable membrane oxygenators, one-half with bubble oxygenators.

1986 — An artificial liver using porcine hepatitides was described by DeMetriou.

1987 — Bard cardiopulmonary support system (CPS) was introduced for rapid deployment, portable, percutaneous access for cardiac emergencies.

1988 — The axial-flow blood pump was described by Wampler at ASAIO.

1994 — FDA approval of the pneumatically driven HeartMate LVAD (Thermo Cardiosystems, Inc.) for bridge to transplantation (the first pump with textured blood-contacting surfaces).

1996 — REMATCH Trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure, E Rose principal investigator) was initiated with HeartMate VE (Thoratec Corp.). Results published in 2002 showed mortality reduction of 50% at one year as compared to patients receiving optimal medical therapy.

1998 — Simultaneous FDA approval of HeartMate VE (ThermoCardiosystems) and Novacor LVAS (Baxter Healthcare Corp), electrically powered, wearable assist systems for Bridge to Transplantation.

1998 — First clinical application of next-generation continuous-flow assist devices. DeBakey (Micromed Inc.) axial-flow pump was implanted by R. Hetzer, G. Noon and M. DeBakey.

1999 — First clinical application of a fully implantable circulatory support system. LionHeart LVAS was implanted in 67 year-old male recipient by R. Koerfer and W. Pae.

Late 1990s — Many surgeons began to use a minimally invasive surgery that requires only a 3-to-5-inch incision. Rather than cutting down the front of the leg, damaging the slow-to-heal thigh muscle, the cuts can be made in the side of the knee, and the kneecap is pushed to the side for access. This technique allowed faster recovery and fewer complications.

2001 — The AbioCor totally implantable, electrically powered TAH is implanted into patient Robert Tools by L. Gray and R. Dowling (clinical trial is ongoing.).

2002 — FDA approval of the HeartMate VE LVAD for permanent use (Thoratec Corporation).

2002 – Dr. C S Ranawat at Lenox Hill Hospital – New York published history of total knee replacements in Journal South Orthopaedic Assoctation (Winter issue, 11(4):218–26). He indicated that "*Today, over 19 companies in the United States distribute total knee implants of three different types: cruciate-preserving, cruciate-substituting, and TC-III. Six major companies are actively involved in designing mobile-bearing knees. Future developments, such as navigation-guided surgery, enhanced kinematics, and wear-resistant bearing surfaces with better fixation, promise a consistent evolution for the total knee replacement*."

2007 <Stanford.edu> released free software for biomechanical modeling: OpenSim 1.0 on August 20, 2007; OpenSim 1.1 on December 11, 2007; OpenSim 2.2.1 on April 11, 2011; and OpenSim on October 10 of 2011.

2009 Unicondylar, or partial, knee replacements were introduced. It causes fewer side effects and loss of blood, because a smaller incision of up to three inches is made. According to the 2009 report by Utah Hip and Knee Center, the research is being done to develop a knee replacement technology in which the bones actually grow into the device and hold it together. Researchers claim that this technology would create fewer complications due to knee replacement surgery.

21st century Orthopaedic surgeons started to use a robotic knee replacement process using a series of CT scans to create a customized knee replacement plan based on the needs of an individual patient. It consists of a computer-assisted planning program and robotic instruments used to make incisions and position implants. The robotic instruments are able to manipulate tools and implants much more accurately than the human eye. Because of the precise nature of this technology, many common knee replacement problems are avoided. <http://echo.gmu.edu/bionics/exhibits.htm>.

1.5 SOCIETIES: ARTIFICIAL ORGANS

<http://www.esao.org/links.php>

- ACC American College of Cardiology
- AIMBE American Institute For Medical and Biological Engineering
- ANNA American Nephrology Nurses Association
- ASAIO American Society for Artificial Internal Organs
- ASAO Austrian Society for Artificial Organs
- EMBS Engineering in Medicine and Biology
- EDTA European Dialysis and Transplantation Association
- ESB European Society for Biomaterials
- ESEM European Society for Enginerring and Medicine
- ISABI International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology
- IFAO International Federation for Artificial Organs – former ISAO
- ISFA International Society for Apheresis
- ISPD International Society for Peritoneal Dialysis
- ISRP International Society for Rotary Blood Pumps
- JSAO Japanese Society for Artificial Organs (japanese version)
- NKF National Kidney Foundation
- TERMIS Tissue Engineering and Regenerative Medicine International

General Medical/Technology <http://www.esao.org/links.php>

- HSTAT Health Services Technology Assessment Texts: Searchable NIH databases on health services and technologies.
- MedEc Interactive The Medical Economics site, with a searchable database of their publications, including the PDR.
- Medical Device Link – An industry-sponsored site full of info: News, publications, suppliers directory, job listings, WWW links, etc.

- National Inventors Hall of Fame
- NIH Technology Assessment Statements Full text search of consensus statements from NIH Technology Assessment Conferences and Workshops
- PubMed Free, fast, and efficient searching of the MEDLINE database. (A service of the National Center for Biotechnology Information (NCBI), which has its own site, well worth visiting.)
- The Visible Human Project "Complete, anatomically detailed, three-dimensional representations of the male and female human body. The current phase of the project is collecting transverse CT, MRI and cryosection images of representative male and female cadavers at one millimeter intervals." A project of the National Library of Medicine.
- WWW Home Pages about Artificial Organs Courtesy of the Japanese Society for Artificial Organs. Most listed sites are in Japan.
- Center for Apheresis Technology

Literature <http://www.esao.org/links.php>

- International Journal for Artificial Organs, published at Wichtig-Verlag
- Journal of Artificial Organs, published at Springer
- Artificial Organs: The Journal of the IFAO
- MediConf®, The Database on Medical Conferences and Exhibitions Worldwide
- Journals of Biomaterials: link-list of several worldwide published journals
- Science-Directory.net: link-list of Science

BIOMEDICAL IMPLANTS

The biomedical implants are the medical devices and structures that are inserted directly into the body of a patient. Whereas the prostheses are commonly attached to the body rather than being inserted into the body. The biomedical engineering industry uses the problem solving application of engineering science to provide better diagnosis and more effective remedies for a variety of medical problems. A biomedical implant popular in the past decades is hip replacement. Although the common patient is over 60 and has undergone serious bone and joint deterioration, the hip implants are also used with younger people that have less than optimum joint mobility. The hip implants have proven to be very effective, giving many people better movement ability and thus improving the quality of life. In some cases, patients may need a second hip replacement procedure due to wear and tear on the implant or other factors. Other common implants are contact lenses that are corrective disks put directly on the eyes to improve the vision. Many different variations of contact lenses have been created to match the different eyesight problems. It is now possible for a set of contact lenses to be specifically created for a particular need.

1.6 PROSTHESIS

In medicine, prosthesis, **prosthetic**, or **prosthetic limb** (from Ancient Greek *prósthesis*, "addition, application, attachment") is an artificial device extension that replaces a missing body part. It is part of the field of biomechatronics: the science of using mechanical devices with human muscle, skeleton, and nervous systems to assist or enhance motor control lost by trauma, disease, or defect. Prostheses are typically used

to replace parts lost by injury (traumatic) or missing from birth (congenital) or to supplement defective body parts. Other medical devices and aids that can be considered prosthetics include hearing aids, artificial eyes, palatal obturator, gastric bands, and dentures.

Prosthetics are specifically not orthotics, although given certain circumstances a prosthetic might end up performing some or all of the same functionary benefits as an orthotic. Prosthesis is technically a complete finished item. For instance, a C-Leg knee alone is not prosthesis, but only a prosthetic part. The complete prosthesis would consist of the stump attachment system – usually a "socket," and all the attachment hardware parts all the way down to and including the foot.

Although prostheses have a history that dates back to the ancient Egyptians and Roman times, it is only in the twentieth century that prostheses with a high degree of effectiveness have been created. Prior to the early 1950s, the prosthetic models were often crude and served a very basic function in replacing a limb that was missing due to birth defects or injuries. After World War II, there has been more awareness about prosthetic improvements and several professional organizations have been created to encourage technology advancements in the prostheses industry, leading to new models that provide a new level of comfort and functional ability for the user. While the vast majority of prostheses exist as a stand alone device that replaces a limb or body part, there are also prosthetic device that interact with the muscles and nervous system of the body. By detecting the neural signals that are sent to the limbs from the brain, a person with a robotic prosthetic arm may be able to control the limb in the same manner that a normal arm would be used. These robotic prostheses also have sensors that can react to force and load, thus creating the best possible equivalent to having the same natural limb.

Hearing aids and artificial eyes are other examples of prostheses that are directly connected to the person's existing nervous system and provide improved function through an exchange of information. In modern times, the latest prosthetic limbs have proven to be even more effective than natural limbs. A case in point is found with the competitive runner, Oscar Pistorius, from South Africa. Using state-of-the-art prosthetic lower legs, Pistorius was denied eligibility to compete in the Summer Olympics competition of 2008. A study of the prosthetic legs found that they were actually more efficient than the competitors with normal legs, using 25% less energy. While this is only one example of how a prosthetic limb has become a more effective option, the advancements in technology are expected to lead to the creation of many prostheses that actually improve the body's function further than its natural limitations. Figure 2a shows a man with two prosthetic arms playing table football.

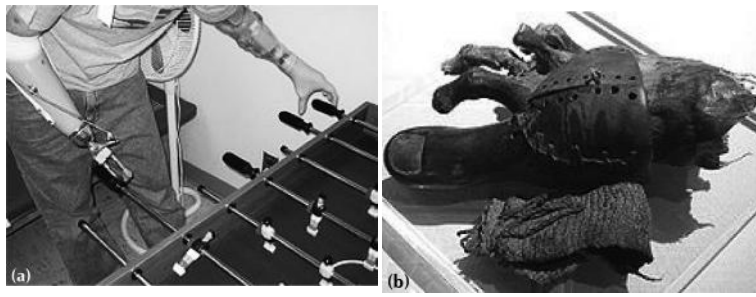


FIGURE 2 (a) A man with two prosthetic arms playing table football; (b) Prosthetic toe from ancient Egypt.

Other major improvements before the modern era are:

- Pieter Verduyn – First nonlocking below-knee (BK) prosthesis.
- James Potts – Prosthesis made of a wooden shank and socket, a steel knee joint and an articulated foot that was controlled by catgut tendons from the knee to the ankle. Came to be known as "Anglesey Leg" or "Selpho Leg."
- Sir James Syme – A new method of ankle amputation that did not involve amputating at the thigh.
- Benjamin Palmer – Improved upon the Selpho leg. Added an anterior spring and concealed tendons to simulate natural-looking movement.
- Dubois Parmlee – Created prosthetic with a suction socket, polycentric knee, and multiarticulated foot.
- Marcel Desoutter and Charles Desoutter – First aluminum prosthesis.

At the end of World War II, the National Academy of Sciences began to advocate better research and development of prosthetics. Through government funding, a research and development program was developed within the Army, Navy, Air Force, and the Veterans Administration. The following organizations were created to help and inform the general public about prosthetics:

- **American Orthotics and Prosthetic Association, American Board for Certification in Prosthetics and Orthotics, American Academy of Orthotics and Prosthetics** – These three educational groups work together and provide certification of individuals and facilities working with orthotics and prosthetics.
- **The International Society for Prosthetics and Orthotics** – Founded in 1970 and headquartered in Copenhagen, this association helps with the progression in research and clinical practice worldwide. They hold an international conference every three years and publish a technical journal.
- **Association of Children's Orthotic-Prosthetic Clinics** – The organization was started in 1950s to advocate research and development of children's prosthetics. They meet annually and publish technical articles.
- **Amputee Coalition of America** – The organization was created in 1990 to improve the lives of amputees. Advocate the improvement of amputee lifestyle through education and publish a magazine: "inMotion."

Socket technology for lower extremity limbs saw a revolution of advancement during the 1980s when John Sabolich invented the "Contoured Adducted Trochanteric-Controlled Alignment Method (CATCAM) socket," later to evolve into the "Sabolich Socket." Prior, sockets were made in the shape of a square shape with no specialized containment for muscular tissue. New designs thus helped to lock in the bony anatomy, locking it into place and distributing the weight evenly over the existing limb as well as the musculature of the patient. Ischial containment is well known and used today by many prosthetist to help in patient care. Variation's of the ischial containment socket thus exists and each socket is tailored to the specific needs of the patient. Others who contributed to socket development and changes over the years include: Tim Staats, Chris Hoyt, and Frank Gottschalk.

The first microprocessor-controlled prosthetic knees became available in the early 1990s. The Intelligent Prosthesis was released by Chas. A. Blatchford & Sons, Ltd., of Great Britain, in 1993. An improved version was released in 1995 by the name Intelligent Prosthesis Plus. Blatchford released the Adaptive Prosthesis, in 1998. The Adaptive Prosthesis used hydraulic controls, pneumatic controls, and a microprocessor to provide the amputee with a gait that was more responsive to changes in walking speed. Little evidence exists to support the tremendous financial burden to third parties who pay essentially the cost of a cheap home for the microprocessor knee, ischial containment socket, flexfoot leg. Some amputees from the Iraq and Afghanistan conflicts have returned to service with sophisticated prostheses. Cost analysis reveals that a sophisticated above knee prosthesis will be in the neighborhood of $1 million in 45 years, given only annual cost of living adjustments.

1.6.1 C-LEG KNEE PROSTHESIS

The Otto Bock orthopedic industry introduced the **C-Leg** during the world congress on orthopedics in Nuremberg in 1997. The company began marketing the C-Leg in the United States in 1999. Other microprocessor-controlled knee prostheses are: Ossur's Rheo Knee, released in 2005; the Power Knee by Ossur, introduced in 2006; the Plié Knee from Freedom Innovations; and DAW Industries' Self Learning Knee (SLK).

The idea was originally developed by Kelly James, an engineer at the University of Alberta. The C-Leg uses hydraulic cylinders to control the flexing of the knee. Sensors send signals to the microprocessor that analyzes these signals, and communicates what resistance the hydraulic cylinders should supply. C-Leg is an abbreviation of 3C100, the model number of the original prosthesis, but has continued to be applied to all Otto Bock microprocessor-controlled knee prostheses. The C-Leg functions through various technological devices incorporated into the components of the prosthesis. The C-Leg uses a knee-angle sensor to measure the angular position and angular velocity of the flexing joint. Measurements are taken up to 50 times a second. The knee-angle sensor is located directly at the axis of rotation of the knee.

Moment sensors are located in the tube adapter at the base of the C-Leg. These moment sensors use multiple strain gauges to determine where the force is being applied to the knee, from the foot, and the magnitude of that force. Figure 3 indicates two different types of C-Leg prostheses.

FIGURE 3 Two different models of the C-Leg prosthesis.

The C-Leg controls the resistance to rotation and extension of the knee using a hydraulic cylinder. Small valves control the amount of hydraulic fluid that can pass into and out of the cylinder, thus regulating the extension and compression of a piston connected to the upper section of the knee.[10] The microprocessor receives signals from its sensors to determine the type of motion being employed by the amputee. The microprocessor then signals the hydraulic cylinder to act accordingly. The microprocessor also records information concerning the motion of the amputee that can be downloaded onto a computer and analyzed. This information allows the user to make better use of the prosthetic.

FIGURE 4 Sgt. Jerrod Fields, a U.S. Army World Class Athlete Program Paralympic sprinter hopeful, works out at the U.S. Olympic Training Center in Chula Vista, Calif. A below-the-knee amputee, Fields won a gold medal in the 100 m with a time of 12.15 sec at the Endeavor Games in Edmond, Okla., on June 13, 2009.

The C-Leg is powered by a lithium-ion battery housed inside the prosthesis near the knee joint. On a full charge, the C-leg can operate for up to 45 hours, depending on the intensity of use. A charging port located on the front of the knee joint can be connected to a charging cable plugged directly into a standard outlet. A "pigtail" charging port adapter permits the relocation of the charging port to a location more accessible when the prosthesis has a cosmetic cover applied. The charger cord has lights that allow the user to observe the level of charge when connected to the knee. A 12 volt car charger adapter can also be purchased.

A wide range of amputees can make use of the C-Leg; however, some people are more suited to this prosthesis than others. The C-Leg is designed for use on people who have undergone transfemoral amputation, or amputation above the knee. The C-Leg can be used by amputees with either single or bilateral limb amputations. In the

case of bilateral amputations, the application of C-Legs must be closely monitored. In some cases, those who have undergone hip disarticulation amputations can be candidates for a C-Leg.[18] The prosthesis is recommended for amputees that vary their walking speeds and can reach over 3 miles per hour; however, it cannot be used for running. The C-Leg is practical for upwards of 3 miles daily, and can be used on uneven ground, slopes, or stairs. Active amputees, such as bikers and rollerbladers may find the C-Leg suited to their needs.

Certain physical requirements must be met for C-Leg use. The amputee must have satisfactory cardiovascular and pulmonary health. The balance and strength of the amputee must be sufficient to take strides while using prosthesis. The C-Leg is designed to support amputees weighing up to 275 pounds.

1.6.2 ROBOTIC PROSTHESES

In order for a robotic prosthetic limb to work, it must have several components to integrate it into the body's function: Biosensors detect signals from the user's nervous or muscular systems. It then relays this information to a controller located inside the device, and processes feedback from the limb and actuator (e.g., position, force) and sends it to the controller. Examples include wires that detect electrical activity on the skin, needle electrodes implanted in muscle, or solid-state electrode arrays with nerves growing through them. Mechanical sensors process aspects affecting the device (e.g., limb position, applied force, load) and relay this information to the biosensor or controller. Examples include force meters and accelerometers. The controller is connected to the user's nerve and muscular systems and the device itself. It sends intention commands from the user to the actuators of the device, and interprets feedback from the mechanical and biosensors to the user. The controller is also responsible for the monitoring and control of the movements of the device. An actuator mimics the actions of a muscle in producing force and movement. Examples include a motor that aids or replaces original muscle tissue.

1.6.3 COSMESIS

Cosmetic prosthesis has long been used to disguise injuries and disfigurements. With advances in modern technology, the creation of lifelike limbs made from silicone or PVC has been made possible. Such prosthetics, such as artificial hands, can now be made to mimic the appearance of real hands, complete with freckles, veins, hair, fingerprints and even tattoos. Custom-made cosmeses are generally more expensive (costing thousands of US dollars, depending on the level of detail), while standard cosmeses come ready-made in various sizes, although they are often not as realistic as their custom-made counterparts. Another option is the custom-made silicone cover, which can be made to match a person's skin tone but not details such as freckles or wrinkles. Cosmeses are attached to the body in any number of ways, using an adhesive, suction, form-fitting, stretchable skin, or a skin sleeve.

1.6.4 NEUROPROSTHETICS

Unlike neuromotor prostheses, neurocognitive prostheses can sense or modulate neural function in order to physically reconstitute or augment cognitive processes such as

executive function, attention, language, and memory. No neurocognitive prostheses are currently available but the development of implantable neurocognitive brain-computer interfaces has been proposed to help treat conditions such as stroke, traumatic brain injury, cerebral palsy, autism, and Alzheimer's disease. The recent field of Assistive Technology for Cognition concerns the development of technologies to augment human cognition. Scheduling devices such as Neuropage remind users with memory impairments when to perform certain activities, such as visiting the doctor. Micro-prompting devices such as PEAT, AbleLink and GUIDE have been used to aid users with memory and executive function problems to perform activities of daily living.

In addition to the standard artificial limb for everyday use, many amputees or congenital patients have special limbs and devices to aid in the participation of sports and recreational activities. Within science fiction, and, more recently, within the scientific community, there has been consideration given to using advanced prostheses to replace healthy body parts with artificial mechanisms and systems to improve function. Body parts such as legs, arms, hands, feet, and others can be replaced. In 2002, British scientist Kevin Warwick did an implant with interfacing directly into Warwick's nervous system. The electrode array, which contained around a hundred electrodes, was placed in the median nerve. The signals produced were detailed enough that a robot arm was able to mimic the actions of Warwick's own arm and provide a form of touch feedback again via the implant.

Figure 4 shows a US military athlete with left leg ampulated who won the gold medal. In early 2008, Oscar Pistorius, the "Blade Runner" of South Africa, was briefly ruled ineligible to compete in the 2008 Summer Olympics because his prosthetic limbs were supposed to give him an unfair advantage over runners who had ankles. One researcher found that his limbs used 20-five percent less energy than those of an able-bodied runner moving at the same speed. This ruling was overturned on appeal, with the appellate court stating that the overall set of advantages and disadvantages of Pistorius' limbs had not been considered. Pistorius did not qualify for the South African team for the Olympics, but went on to sweep the 2008 Summer Paralympics, and has been ruled eligible to qualify for any future Olympics. He qualified for the 2011 World Championship in South Korea and reached the semifinal where he ended last timewise, he was 14th in the first round. Dean Kamen's company DEKA developed the "Luke arm," an advanced prosthesis currently under trials as of 2008.

1.6.5 TRANSTIBIAL PROSTHESIS

A transtibial prosthesis is an artificial limb that replaces a leg missing below the knee. Transtibial amputees are usually able to regain normal movement more readily than someone with a transfemoral amputation, due in large part to retaining the knee, which allows for easier movement. In the prosthetic industry a transtibial prosthetic leg is often referred to as a "BK" or below the knee prosthesis. The majority of prosthetic devices are for below the knee amputees an intimate socket fit will provide improved comfort and gait patterns. Prosthetic devices commonly use silicone; urethane or elastomeric gels fit directed to the residual limb and hold the prosthetic device with or without pin locks. Elevated vacuum socket use is also on the rise and the intimate fit provides better blood flow to the residue limb for greater limb health for the amputee.

1.6.6 TRANSFEMORAL PROSTHESIS

A transfemoral prosthesis is an artificial limb that replaces a leg missing above the knee. Transfemoral amputees can have a very difficult time regaining normal movement. In general, a transfemoral amputee must use approximately 80% more energy to walk than a person with two whole legs. This is due to the complexities in movement associated with the knee. In newer and more improved designs, after employing hydraulics, carbon fiber, mechanical linkages, motors, computer microprocessors, and innovative combinations of these technologies to give more control to the user. In the prosthetic industry a transfemoral prosthetic leg is often referred to as an "AK" or above the knee prosthesis.

1.6.7 TRANSRADIAL PROSTHESIS

A transradial prosthesis is an artificial limb that replaces an arm missing below the elbow. Two main types of prosthetics are available. Cable operated limbs work by attaching a harness and cable around the opposite shoulder of the damaged arm. The other form of prosthetics available is myoelectric arms. These work by sensing, via electrodes, when the muscles in the upper arm moves, causing an artificial hand to open or close. In the prosthetic industry a transradial prosthetic arm is often referred to as a "BE" or below elbow prosthesis.

1.7.8 TRANSHUMERAL PROSTHESIS

A transhumeral prosthesis is an artificial limb that replaces an arm missing above the elbow. Transhumeral amputees experience some of the same problems as transfemoral amputees, due to the similar complexities associated with the movement of the elbow. This makes mimicking the correct motion with an artificial limb very difficult. In the prosthetic industry a transhumeral prosthesis is often referred to as a "AE" or above the elbow prothesis.

1.6.9 CURRENT TECHNOLOGY/MANUFACTURING PROSTHESES

In recent years there have been significant advancements in artificial limbs. New plastics and other materials, such as carbon fiber, have allowed artificial limbs to be stronger and lighter, limiting the amount of extra energy necessary to operate the limb. This is especially important for transfemoral amputees. Additional materials have allowed artificial limbs to look much more realistic, which is important to transradial and transhumeral amputees because they are more likely to have the artificial limb exposed.

In addition to new materials, the use of electronics has become very common in artificial limbs. **Myoelectric limbs**, which control the limbs by converting muscle movements to electrical signals, have become much more common than cable operated limbs. Myoelectric signals are picked up by electrodes, the signal gets integrated and once it exceeds a certain threshold, the prosthetic limb control signal is triggered which is why inherently, all myoelectric controls lag. Conversely, cable control is immediate and physical, and through that offers a certain degree of direct force feedback that myoelectric control does not. Computers are also used extensively in the manufacturing of limbs. Computer Aided Design and Computer Aided Manufacturing are often used to assist in the design and manufacture of artificial limbs.

Most modern artificial limbs are attached to the stump of the amputee by belts and cuffs or by suction. The stump either directly fits into a socket on the prosthetic, or — more commonly today — a liner is used that then is fixed to the socket either by vacuum (suction sockets) or a pin lock. The softness of liners help to create a far better suction fit than hard sockets. Silicone liners can be obtained in standard sizes, mostly with a circular (round) cross section, but for any other stump shape, custom liners can be made. The socket is custom made to fit the residual limb and to distribute the forces of the artificial limb across the area of the stump (rather than just one small spot), which helps reduce wear on the stump. The custom socket is created by taking a plaster cast of the stump or, more commonly today, of the liner worn over the stump, and then making a mold from the plaster cast. Newer methods include laser guided measuring which can be input directly to a computer allowing for a more sophisticated design.

There is a problem with the stump and socket attachment due to a bad fit that will reduce the area of contact between the stump and socket or liner, and increase pockets between stump skin and socket or liner. This exerts high pressure thus causing a pain. Air pockets can allow sweat to accumulate that can soften the skin. Ultimately, this is a frequent cause for itchy skin rashes. Further down the road, it can cause breakdown of the skin. Artificial limbs are typically manufactured using the following steps:

- Measurement of the stump.
- Measurement of the body to determine the size required for the artificial limb.
- Fitting of a silicone liner.
- Creation of a model of the liner worn over the stump.
- Formation of thermoplastic sheet around the model – This is then used to test the fit of the prosthetic.
- Formation of permanent socket.
- Formation of plastic parts of the artificial limb: Different methods are used, including vacuum forming and injection molding.
- Creation of metal parts of the artificial limb using die casting.
- Assembly of entire limb.

Current body powered arms contain sockets that are built from hard epoxy or carbon fiber. Wrist units are either screw-on connectors featuring the UNF 1/2–20 thread (USA) or quick release connector. Terminal devices contain a range of hooks, hands or other devices. Hands require a large activation force, which is often uncomfortable. Hooks require a much lower force. Mechanical hands are sold by Hosmer and Otto Bock. The Becker Hand is still manufactured by the Becker family. Prosthetic hands may be fitted with standard stock or custom-made cosmetic looking silicone gloves. But regular work gloves may be worn as well. Other terminal devices include: V2P Prehensor; a versatile robust gripper that allows customers to modify aspects of it; Texas Assist Devices (with a whole assortment of tools); and TRS that offers a range of terminal devices for sports. Cable harnesses can be built using aircraft steel cables, ball hinges and self-lubricating cable sheaths. Current high tech allows body powered arms to weigh around half to only a third of the weight that a myoelectric arm has.

A **myoelectric prosthesis** uses electromyography signals or potentials from voluntarily contracted muscles within a person's residual limb on the surface of the skin to control the movements of the prosthesis, such as elbow flexion/extension, wrist supination/pronation (rotation) or hand opening/closing of the fingers. Prosthesis of this type uses the residual neuro-muscular system of the human body to control the functions of an electric powered prosthetic hand, wrist or elbow. This is as opposed to an electric switch prosthesis, which requires straps and/or cables actuated by body movements to actuate or operate switches that control the movements of prosthesis or one that is totally mechanical. It is not clear whether those few prostheses that provide feedback signals to those muscles are also myoelectric in nature. It has a self suspending socket with pick up electrodes placed over flexors and extensors for the movement of flexion and extension respectively. The first commercial myoelectric arm was developed in 1964 by the Central Prosthetic Research Institute of the USSR, and distributed by the Hangar Limb Factory of the UK.

Robotic limbs: Advancements in the processors used in myoelectric arms has allowed for artificial limbs to make gains in fine tuned control of the prosthetic. The Boston Digital Arm allows movement in five axs and allows the arm to be programed for a more customized feel. Recently the i-Limb hand has become the first commercially available hand prosthesis with five individually powered digits. The hand also possesses a manually rotatable thumb which is operated passively by the user and allows the hand to grip in precision, power and key grip modes. Raymond Edwards, Limbless Association Acting CEO, was the first amputee to be fitted with the i-LIMB by the National Health Service in the UK. Another neural prosthetic is Johns Hopkins University Applied Physics Laboratory Proto 1. Besides the Proto 1, the university also finished the Proto 2 in 2010.

Robotic legs: The Argo Medical Technologies ReWalk is an example or a recent robotic leg, targeted to replace the wheelchair. It is marketed as a "robotic pants."

Targeted muscle reinnervation (TMR) is a technique in which motor nerves which previously controlled muscles on an amputated limb are surgically rerouted so that they reinnervate a small region of a large, intact muscle, such as the pectoralis major. As a result, when a patient thinks about moving the thumb of his missing hand, a small area of muscle on his chest will contract instead. By placing sensors over the reinervated muscle, these contractions can be made to control movement of an appropriate part of the robotic prosthesis.

Targeted sensory reinnervation (TSR): This procedure is similar to TMR, except that sensory nerves are surgically rerouted to skin on the chest, rather than motor nerves rerouted to muscle. The patient feels any sensory stimulus on that area of the chest, such as pressure or temperature, as if it were occurring on the area of the amputated limb which the nerve originally innervated. In the future, artificial limbs could be built with sensors on fingertips or other important areas. When a stimulus, such as pressure or temperature, activated these sensors, an electrical signal would be sent to an actuator, which would produce a similar stimulus on the "rewired" area of chest skin. The user would then feel that stimulus as if it were occurring on an appropriate part of the artificial limb.

Recently, robotic limbs have improved in their ability to take signals from the human brain and translate those signals into motion in the artificial limb. DARPA, the Pentagon's research division, is working to make even more advancements in this area, with an objective to create an artificial limb that ties directly into the nervous system.

Osseointegration is a new method of attaching the artificial limb to the body. This method is also sometimes referred to as exoprosthesis (attaching an artificial limb to the bone), or endo-exoprosthesis. The stump and socket method can cause significant pain in the amputee, which is why the direct bone attachment has been explored extensively. The method works by inserting a titanium bolt into the bone at the end of the stump. After several months, the bone attaches itself to the titanium bolt and an abutment is attached to the titanium bolt. The abutment extends out of the stump and the artificial limb is then attached to the abutment.

1.6.10 COST

Transradial and transtibial prostheses typically cost between US $6,000 and $8,000. Transfemoral and transhumeral prosthetics cost approximately twice as much with a range of $10,000 to $15,000 and can sometimes reach costs of $35,000. The cost of an artificial limb does recur because artificial limbs are usually replaced every 3–4 years due to wear and tear. In addition, if the socket has fit issues, the socket must be replaced within several months. If height is an issue, components can be changed.

"Low cost above knee prostheses" often provide only basic structural support with limited function. This function is often achieved with crude, nonarticulating, unstable, or manually locking knee joints. A limited number of organizations, such as the International Committee of the Red Cross (ICRC), create devices for developing countries. Their device which is manufactured by CR Equipments is a single-axis, manually operated locking polymer prosthetic knee joint. The available technologies for knee joint are listed in Table 1.

TABLE 1 Available technologies for knee joint.

Technology country of origin)	Description	Highest level of evidence
ATLAS knee (UK)	Weigh-activated friction	Independent field
DAV/Seattle knee (US)	Compliant polycentric	Field
Friction knee (US)	Weigh-activated friction	Technical development
Friction knee (US)	Weigh-activated friction	Technical development
ICRC knee (Switzerland)	Single-axis with manual lock	Independent field
JaipurKnee (India)	Four-bar	Field
LCKnee (Canada)	Single-axis with automatic lock	Field
LEGS M1 knee (US)	Four-bar	Field

TABLE 1 *(Continued)*

Technology country of origin)	Description	Highest level of evidence
None provided (India)	Six-bar with squatting	Technical development
None provided (Nepal)	Single-axis	Field
None provided (New Zealand)	Roto-molded single-axis	Field
POF/OTRC knee (US)	Single-axis with ext. assist	Field
SATHI friction knee (India)	Weigh-activated friction	Limited data available
Wedgelock knee (Australia)	Weigh-activated friction	Technical development

There is currently an open Prosthetics design forum known as the "Open Prosthetics Project." The group employs collaborators and volunteers to advance Prosthetics technology while attempting to lower the costs of these necessary devices. A plan for a low-cost artificial leg, designed by Sébastien Dubois, was featured at the 2007 International Design Exhibition and could be available for US $8.00, composed primarily of fiberglass.

Prior to the 1980s, foot prostheses merely restored basic walking capabilities. These early devices can be characterized by a simple artificial attachment connecting one's residual limb to the ground.

The introduction of the Seattle Foot (Seattle Limb Systems) in 1981 revolutionized the field, bringing the concept of an Energy Storing Prosthetic Foot (ESPF). Soon, there were multiple models of energy storing prostheses on the market. Each model used some variation of a compressible heel. The heel is compressed during initial ground contact, storing energy, which is then returned during the latter phase of ground contact to help propel the body forward. Since then, the foot prosthetics industry has been dominated by steady, small improvements in performance, comfort, and marketability. Jaipur Foot from India costs about US$ 40.

1.6.11 DESIGN CONSIDERATIONS

There are multiple following factors to consider when designing a transtibial prosthesis:

- Performance.
- Nonetheless, there are certain elements of foot mechanics that are invaluable for the athlete, and these are the focus of today's high-tech prosthetics companies:
  - Energy storage and return – storage of energy acquired through ground contact and utilization of that stored energy for propulsion.
  - Energy absorption – minimizing the effect of high impact on the musculoskeletal system.
- Ground compliance – stability independent of terrain type and angle.
- Rotation – ease of changing direction.
- Weight – maximizing comfort, balance and speed.
- Suspension – how the socket will join and fit to the limb.
- Other: Cosmetics; Cost; Ease of use; and Size availability.

KEYWORDS

- **Anglesey Leg**
- **Artificial Organ**
- **Biomechanics**
- **C-Leg Knee Prosthesis**
- **Myoelectric Limbs**
- **Neuroprosthetics**
- **Robotic Legs**
- **Robotic Limbs**
- **Robotic Prostheses**
- **Sabolich Socket**
- **Selpho Leg**
- **Transfemoral Prosthesis**
- **Transhumeral Prosthesis**
- **Transradial Prosthesis**
- **Transtibial Prosthesis**

CHAPTER 2

BIOFLUID DYNAMICS OF CARDIOPULMONARY BYPASS SURGERY[1, 2]

CONTENTS

[1]This chapter has been modified from the review article that was prepared by the students (Jesse L. Castillo, Victor Delgado, John Ramirez and Karym Urdanet) for the course on Biofluid Mechanics, BME 4994. Course Instructor: Megh R. Goyal, PhD, PE, Visiting Professor in Biomedical Engineering (2003), Biomedical Engineering Department, Florida International University, Miami, FL, USA. For details contact at <goyalmegh@gmail.com> or visit: http://www.ece.uprm.edu/~m_goyal/home.htm. We acknowledge the contribution by the faculty of biomedical engineering at FIU

[2]The numbers in parenthesis refer to bibliographical references with cited pages.

2.1 INTRODUCTION

Cardiovascular disease, principally heart disease and stroke, is the Nation's leading killer with mortality rate of about 42% (18). Under some of the procedures pertaining to cardiovascular diseases – such as open-heart surgery, aortic aneurysm stenting procedure, grafting, and so on there are many specialized devices as well as instrumentation for reducing the mortality risks during surgery. For instance, a person with a high fat diet and other risk factors such as diabetes, smoking, and high blood pressure will develop a condition called atherosclerosis, or plaque formation in the arteries. This condition that involves the hardening and blocking of many arteries, including the coronary arteries, will go through a process called coronary artery bypass grafting (CABG) to eradicate or lessen the hardening of the arteries. CABG and the repair of most cardiac conditions require the cardiothoracic surgeon to work in a bloodless and motionless environment (16). In an open-heart surgery, physicians use a cardiopulmonary bypass (CPB) system to facilitate the surgery and to reduce risk. CPB provides a control environment for cardiovascular surgery by relieving the heart and lungs of their normal life sustaining functions. In this chapter, we will discuss physical and chemical properties of fluids in CPB; principles, applications and procedures of CPB.

2.2 HISTORICAL BACKGROUND

The idea of maintaining the viability of the organs through the infusion of blood had been suggested in the early part of the 19th century. But the development of the heart-lung machine could not have been possible without the help of many John Gibbon and many other researchers.

1931: Like many medical advances, the development of the heart-lung machine depended heavily on animal research. In 1931, John Heysham Gibbon was moved by the death of a patient during cardiac surgery. He was convinced that the patient would have survived if their blood circulation had been artificially maintained. He began to investigate the possibility of building an external device that could do the job of the heart and lungs for short intervals. Gibbon made it his mission to come up with an artificial heart-lung machine that would keep a patient alive during heart surgery.

1930s: During this time, physicians were looking into the possibility of extracorporeal circulation, or blood flow outside of the body. They wondered if there was a way to extend this extracorporeal circulation to bypass not just minor organs, as was often done in surgery at the time, but to bypass the heart completely.

1934: Between 1934 and 1935, Gibbon built a prototype of his heart-lung machine and tested its function on cats in order to assess what problems needed to be addressed before using it with humans. For example, in one model Gibbon observed that an inadequate amount of blood flow was exiting the machine, so he decided to make the flow continuous, instead of in short pulses. By introducing blood flow that would remain at the same rate continuously, instead of increasing and decreasing with a set rhythm, he increased the total blood volume capacity that could flow throughout the machine.

1935: Gibbon and his wife carried out their initial research using cats. By 1935, they developed a machine that could replace the function of heart and lungs of a cat for 20 min. These early animal experiments allowed Gibbon to test different types of pumps and oxygenators to improve the performance. However, the machine damaged the blood cells, and most cats lived no longer than 23 days after surgery. He built the first heart-lung machine in 1937 and had sufficient capacity to perfuse organs in cats.

1945: In the 1940s, Dr. Gibbon met Thomas Watson, an engineer and chairman of International Business Machines (IBM). Watson provided both financial and technical support to Gibbon to develop a heart-lung machine. Both collaborated on the quest for an effective cardiopulmonary bypass machine, and together they created a new model. When this model was tested by performing surgeries on dogs, they noticed that many of their test subjects died after surgery due to embolisms (An embolism occurs when a small particle or tissue migrates to another part of body and causes the blockage of a blood vessel, which prevents vital tissues from receiving oxygen). From these experiments, they saw the need to add a filter to their apparatus. Gibbon and the IBM engineers decided to use a 300 × 300-micron mesh filter, which proved successful in trapping these harmful tissue particles.

1946: Watson along with five other IBM engineers helped Gibbon to invent a machine that minimized haemolysis and prevented air bubbles from entering the circulation. This heart-lung machine was contained within a cabinet that kept the body at normal temperature and blood flow was carefully controlled to maintain a constant blood supply. With the invention of this machine, the mortality rate in dogs was reduced from 80% to 10%. Once these issues were addressed, most dogs survived their open heart surgery, and the heart-lung machine was ready for use in humans.

1953: John Gibbon realized his 20-year vision and performed the first successful operation on a human using the heart-lung machine. The patient, Cecelia Bavolek, whose heart was connected to the machine for 45 min, recovered fully from the operation. However, the technique still had a major flaw: The heart was left beating during surgery with some blood still reaching the heart, and this made it messy and made the operation difficult. The problem was again investigated using animals. Experiments in dogs and rabbits showed that the heart could be stopped during surgery for around 15 min and then successfully started again without causing any ill-effects. Complicated heart surgeries required the heart to be stopped for far longer than 15 min, but leaving the heart without blood for such lengthy periods led to serious tissue damage. Extensive testing in rats gave good results. Since then, open heart surgeries have been performed for over 60 years. Much has changed since Gibbon's first model, but the main engineering concepts behind his machine have remained the same.

1960: Bill Bigelow used cooling blankets and ice bags to cool the dogs to 20°C. The oxygen consumption of the heart fell to 15 percent of normal, and thus isolating the heart for the operation with 15 min of allowed time and a better survival rate than previously found. Hypothermia alone, proved unreliable due to the attendant risks of ventricular fibrillation and the limiting short time in which surgery had to be performed without incurring irreversible cerebral anoxia. The heart and other organs are more

tolerant to anoxia than the brain. Using a method to perfuse the brain while the heart was arrested, surgeons were not limited to six minute period or less of cerebral anoxia in which they had to complete intracardiac repairs. Gibbon demonstrated this during a 26-minute operation with CPB on an 18-year-old girl. In 1960, it was considered safe to use the CPB along with hypothermia to perform CABG surgery. Heat exchangers were used to cool and rewarm the blood.

1980s: Researchers at Hospital in St Thomas found that by cooling the heart to below 28°C and treating it with the right cocktail of chemicals, the heart could be stopped for many hours while intricate surgeries were performed, and then restarted with minimal damage. A similar cocktail of chemicals is now used to keep hearts healthy while they are transported for transplantation.

2013: Today, the heart lung-machine, which was invented and perfected through a series of animal experiments, is commonly used to do the job of the heart and lungs for many hours, enabling complex and time-consuming cardiac surgeries to take place. The machine is also essential for keeping patients alive during heart transplants. Today's heart-lung-machine contains the same basic components: a reservoir for oxygen-poor venous blood, an oxygenator, a temperature regulator, a pump to drive the blood flow back to the body, a filter to prevent embolisms, and connective tubing to tie all the other elements together.

2.3 CARDIOPULMONARY BYPASS SYSTEM

The cardiovascular system transports oxygen and other nutrients to all parts of the body. It also removes and disposes of the waste products of metabolism, including carbon dioxide. The circulatory system of the body consists of three major components: the heart, the blood vessels, and the blood. The blood vessels are compared to a tubing system that circulates the blood. In this tubing system there are three mayor types of vessels: the arteries, veins, and capillaries (Figure 1). In this circulatory system there are also two types of circulation: the systemic and pulmonary. The aorta arches from the top of the heart and descends through the trunk of the body until bifurcating in the abdomen.

The arterial system transports the oxygenated blood, while the veins carry the deoxygenated blood back to the heart. The superior vena cava delivers blood from the head and upper body, while the inferior vena cava returns blood from the lower body. The arterial system and the venous system are interconnected at the capillaries. In the capillaries, once oxygen has been used from the blood; blood is returned through the veins where it is collected at the two vena cava. The circulatory loop is completed by a second arterial-venous system imbedded in the lungs, where the capillary beds are the site of blood reoxygenation. Figure 1 shows the path of blood flow.

2.3.1 PRELIMINARY MODEL OF THE CARDIOPULMONARY BYPASS CIRCUIT

The CPB intends to resemble functions of the lungs and heart during a cardiovascular surgery. The heart-lung machine is an apparatus that permits the heart to be operated on safely, by maintaining the circulation of oxygenated blood throughout

the cardiovascular system. The machine is made up of an oxygenator and a pump. The oxygenator repeatedly draws off blood from the veins, reoxygenates, and pumps it back into the arterial system. The simplified models of CPB are shown in Figures 2 and 3.

2.4 PROCEDURES IN CPB

CPB has been performed for nearly 60 years and more than 600,000 bypass surgeries are performed each year in the United States, making it the most frequently performed major surgery. Bypass surgery is a major operation that usually lasts between two to six hours (19). During bypass surgery, the chest bone is separated, and the ribs are spread apart to allow visible and physical access to the heart. The most common incision is the median sternotomy. The sternum is cut with a saw and, immediately beneath the sternum is the pericardium, which must be incised to expose the heart. The sternum is wired with five to six stainless steel wires and these are usually left in situ (in place).

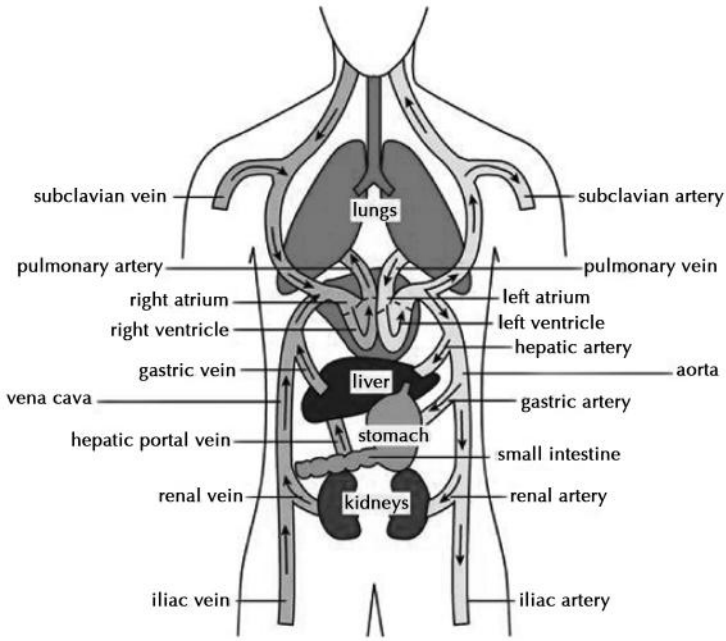


FIGURE 1 Circulatory System.

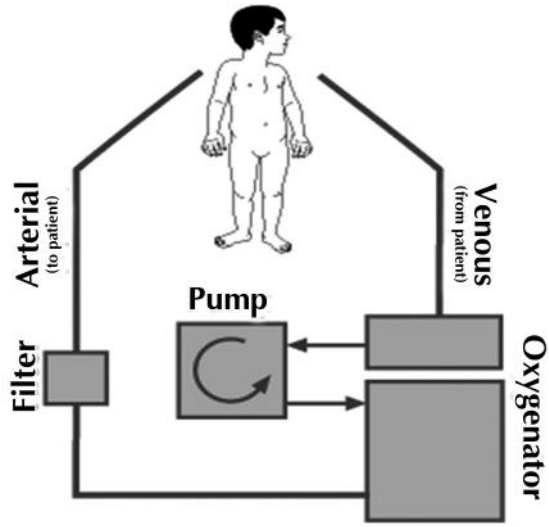


FIGURE 2 CPB Simplified Model.

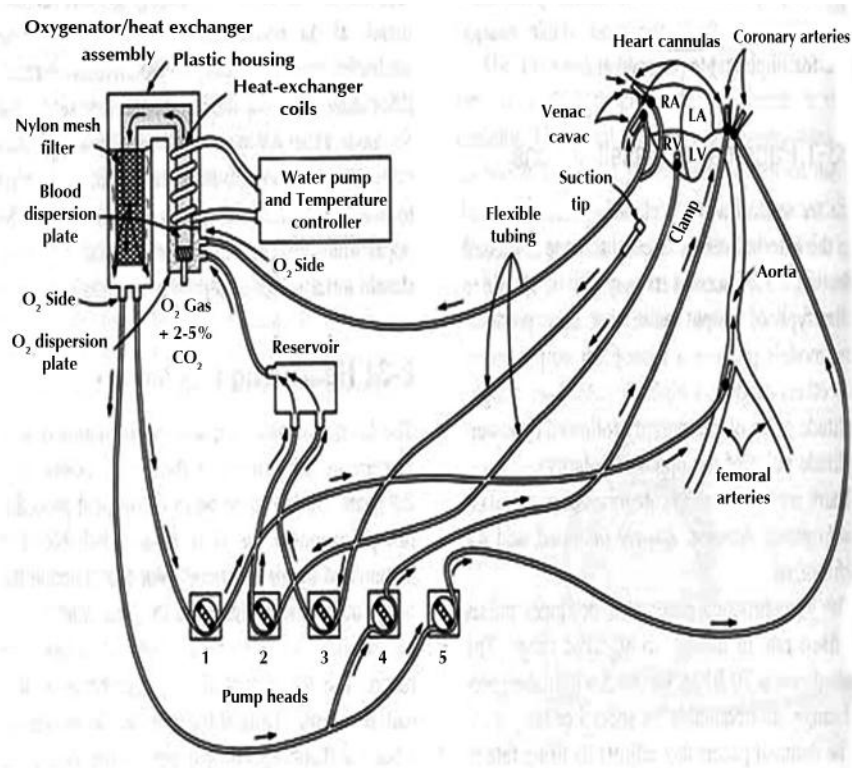


FIGURE 3 Simplified CPB circuit.

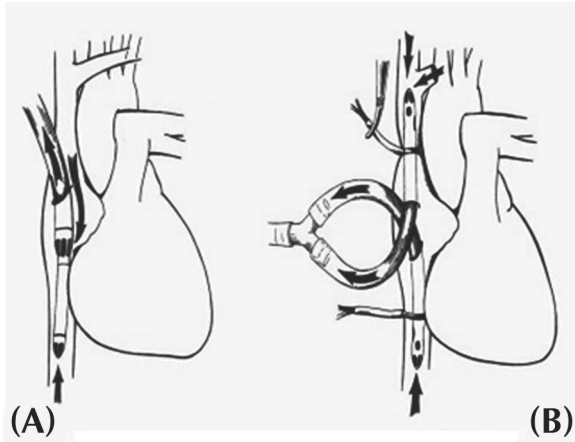


FIGURE 4 Drawings of conventional venous cannulae: **A.** Two stage cavoatrial cannula. **B.** Wire reinforced cannula for atrial or caval cannulatin. **C.** Cannula with right-angle tip (often used for congenital or pediatric cases).

Drains are usually placed to the opened pleural and pericardial cavities and the pericardium is usually left open (20). The heart-lung machine is operated by a perfusionist. The perfusionist is responsible for the selection and set-up of the circuit components for the procedure. The perfusionist works closely with the surgeon and anesthetist (25). Before the operation is performed, the patient is conditioned and prepared with different drugs which are considered later. The surgeon begins the surgery with cannulation.

2.4.1 VENOUS CANNULATION AND DRAINAGE

The usual method for venous drainage is using gravity siphonage. However, suction applied to the venous lines is of renewing interest. This technique had been discarded early in the history of CPB. There are two constraints in siphonage draining. First the level of the venous reservoir must be under the level of patient. Second, the lines must be full of fluid or blood, or else there could be an air lock and it can disrupt the siphonage effect. The amount of venous drainage is determined by the resistance in the venous cannulas, connectors and clamps. It also depends on the difference in height of the patient and reservoir.

Venous cannulas are either single or two stages (cavoatrial). The latter have a wider portion with holes in the section designed to sit in the RA and a narrower tip designed to rest in the IVC (Figure 4). Most cannulas are wire reinforced to prevent kinking and are usually made of a flexible plastic. Some are built out of hard plastic or even metal for optimal inner to outer diameter ratio. The venous cannulas are the narrowest components in the CPB and therefore provide a limitation to the drainage. If the flowing characteristics of the catheter and the total flow (one third of total flow from SVC and two thirds of total flow in IVC) are known, then the appropriate cannula can be selected. The venous connection for CPB is accomplished by inserting cannulas into the RA. Three basic approaches are used.

Bicaval procedure involves insertion of two separate cannulas into SVC and IVC. When bicaval cannulas are used, tapes are commonly placed around the cavae and passed through small tubes so they may be cinched down as tourniquets or snares around the cannula. This forces the entire patient's venous return to pass to the extracorporeal circuit, preventing any blood or air back into the system. This is referred to as caval occlusion, or total CPB. Other methods of occlusion include using elastic tapes placed around the cavae and held together with vascular clips and the use of specially designed external clamps that go around the cavae and their contained cannulas. When there is an orifice in the atrium and it is not possible to insert a purse-string suture or the suture breaks, a cuffed endotracheal tube may also be used for venous drainage. After insertion, the cuff is inflated and gentle traction tamponades the hole in the atrium so proper venous drainage may be provided.

The single atrial cannulation is simpler, faster and less traumatic, with one less incision, and provides fairly good drainage of both the cavae and the right heart.

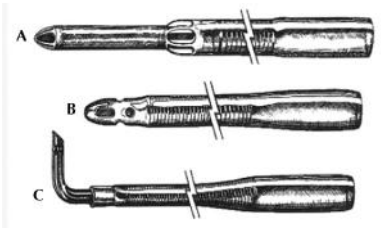


FIGURE 5 Methods of venous cannulation: **A.** Cavaoatrial cannulation with a two-stage cannula. **B.** Bicaval cannulation with two cannulas.

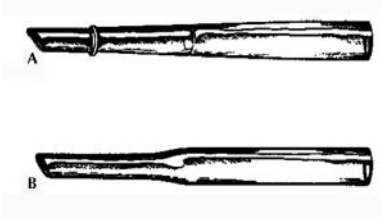


FIGURE 6 A. Bevel-tipped tapered with molded flange. **B.** Cannula without flange "Bardic."

The cavoatrial cannula has many advantages of a single right atrial cannula but may provide better drainage of the right heart. Although drainage of the IVC remains good with cavoatrial cannulation in the circumflex position, drainage of the SVC is compromised. To optimize draining; it is necessary to have atrial holes in the precise location, and the adequacy of decompression of the right heart plus temperature must be appropriately monitored, in order to adjust when needed. Figure 4 shows various cannulas while Figure 5 shows the optimal procedures to be used in corresponding surgeries (4:71).

2.4.2 ARTERIAL CANNULATION

There are many types of cannulas available in the market. They are made of various materials and designed for insertion into the ascending aorta with right angle tips; some are tapered; and some have flanges to aid in fixation and prevention of over insertion. Figures 6 and 7 show examples of types of cannulas. High flow through narrow cannulas may lead to high gradients, high velocity of flow (jets), turbulence and cavitation with undesirable consequences. When evaluating arterial cannulas, it is necessary to consider the pressure drop. A useful characteristic of an arterial cannula is its performance index (pressure gradient versus OD at any given flow). The narrowest part of the catheter that enters the aorta should be as short as compatible for safety, and thereafter the cannula size should enlarge to minimize the gradient. Long catheters with a uniform narrow diameter are undesirable. The use of metal and hard plastic is desirable due to the ID-to-OD ratio. Pressure gradients exceeding 100 mm Hg are associated with excessive hemolysis and protein denaturation. New approaches to hemodynamic evaluation of arterial cannula include velocimetry and detailed analysis of flow patterns using laser Doppler anemometry, color Doppler ultrasound, and high-field magnetic resonance imaging, but the clinical and high-field magnetic resonance imaging, but the clinical use of these studies is yet to be demonstrated. The jet effects can damage the aortic wall, dislodge atheroemboli and cause arterial dissections and disturb flow into nearby vessels. To reduce this effect, a new aortic cannula that has a closed tip and internal cone designed to reduce exit forces and velocities has been introduced. In the old times, arterial inflow was via the subclavian or femoral artery.

Inserting the cannula inserted in the ascending aorta has several advantages over the femoral or iliac arteries. These include ease, safety, and the fact that it does not require an additional incision. The site for cannulation is selected based on the type of cannula to be used, the operation planned, and the quality of the aortic wall. Surgeons have traditionally used a palpation method to detect the site of cannulation, cross clamping and so on. However, this method is much less sensitive and accurate than epivascular ultrasonic scanning. Mills and Everson recommended using a 10 to 20-sec period of venous inflow occlusion to reduce systemic arterial pressure to 40 to 50 mm Hg to improve the reliability of palpation of the ascending aorta (3:77).

Silicone rubber and latex rubber tubing sometimes were used in roller pumps in the past; however, spallation and blood incompatibility are respective problems. New formulations of polyvinyl chloride are being developed for use in roller pumps to minimize spallation. Disposable clear polycarbonate connectors with smooth nonwettable inner surfaces that make smooth junctions with plastic tubing (to minimize turbulence) are desirable. Smooth curves rather than sharp-angled bends will minimize turbulence. Connections must be tight enough to prevent leakage of blood when exposed to positive pressures (up to 500 mm Hg beyond the systemic flow pump) and aspiration of air on the venous side. Table 1 indicates how the tube size varies with flow rate.

2.4.3 PUMPS

The most commonly used pumps in CPB are roller pumps and centrifugal pumps. For the past five decades, roller pumps were the most accepted pumps for CPB. However, recent improvements in centrifugal pumps have resulted in their increased popularity.

Roller pumps compress a segment of the blood-filled tubing. Blood is then pushed ahead of the moving roller. This is accomplished by placing a portion of the tubing inside a curved raceway. This raceway is placed around the ends of rotating arms with rollers. The output of the roller pump is determined by revolutions per minute of the rotating arms and the volume displaced per revolution. Excessive compression of the tubing in a roller pump increases the risk of spallation and hemolysis. Another problem with this pump is its ability to generate exceedingly high pressures in the circuit when the outflow is blocked (4).

Centrifugal pumps have replaced roller pumps at many institutions; mainly because they cannot over pressurize the CPB system (see Figure 8). There is a lower risk of blood trauma and massive air emboli than with roller pumps. These pumps are made of a plastic housing that contains either a fanned impeller or a nest of smooth plastic cones.

Magnets are attached to the impellers and spin in conjunction with another magnet spinning in the drive console. As the impellers spin, a higher pressure is created in the pump than at the inlet port. This causes blood to flow through the pump. Flow rates for these pumps are more difficult to determine than with roller pumps. This is because flow rates can vary with changes in the preload and the afterload, despite a constant rotational speed. For this reason a flow meter is always needed with a centrifugal pump. Another concern with centrifugal pumps is that a return flow can occur if the pump stops.

The pumping action of the heart can never be duplicated by the roller or centrifugal pump, partly because the heart beats to produce a strong pulse. Pulsatile pumps have been made with an indwelling intraaortic balloon pump, an extracorporeal balloon pump, ventricular-type pneumatic or hydraulic pumps, modified roller pumps, and modified centrifugal pumps (4).

2.4.4 OXYGENATORS

Oxygenators not only supply vital oxygen for the blood, but also transport carbon dioxide, anesthetics and other gases into and out of the circulation. The diffusion of gases into blood is dependent on the partial pressure difference of the particular gas. Gas exchange in an oxygenator is never as good as the human lung because the distance for oxygen diffusion in an oxygenator is greater and the surface area for gas exchange is much smaller. However, during CPB a patient undergoes hypothermia, muscle paralysis and anesthesia. These conditions reduce metabolic requirements of the patient and allow oxygenators to provide sufficient gas exchange during CPB.

Although numerous types of oxygenators have been used in the past, including heterologous and homologous biologic lungs, vertical screens, and disc oxygenators. Currently only two varieties are in use: bubble oxygenators and membrane oxygenators. Membrane oxygenators (Figure 9) are used more world wide, while bubble oxygenators are rarely used. The oxygenator does influence the configuration of the extracorporeal circuit, and often the oxygenator includes other components of the circuit. The heat exchanger is usually an integral part of the oxygenator and usually is situated just proximal to the gas exchanging section, or sometimes within the bubble chamber of a bubble oxygenator. Bubble oxygenators are positioned proximal to the pump and include an

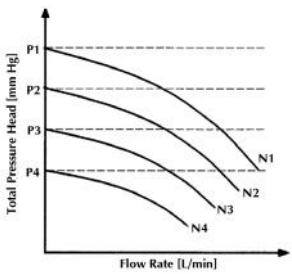
arterial reservoir, which is located distal to the oxygenating column and defoaming area and proximal to the arterial pump for which it serves as an 'atrium.' No additional venous reservoir is included in this circuit since the venous return empties directly into the oxygenating column of the oxygenator, as does the cardiotomy reservoir.

Membrane oxygenators are usually positioned after the pump because the resistance in most membrane oxygenators requires blood to be pumped through them. A venous reservoir receives the venous return, as well as the drainage from the cardiotomy reservoir, and serves as the atrium for the arterial pump, which pumps the blood through the oxygenator and into the patient. Some low-resistance membrane oxygenators may be adequately perfused by gravity drainage of venous blood and, hence, positioned like a bubble oxygenator. For pulsatile bypass with a membrane oxygenator circuit, a second pulsatile pump is placed beyond the membrane oxygenator to avoid the damping that would occur if it were placed proximal to the membrane oxygenator. It requires inclusion of a second (arterial) reservoir and a bypass line to handle the excess flow of the first (venous) pump which must run slightly faster than the arterial pump. If there is no arterial reservoir between the membrane oxygenator and the arterial pump, here is a risk of drawing bubbles of gas across the membrane and into the bypass circuit.

TABLE 1 Effects of diameter of a tube on priming volume and maximum flow rates.

Tubing size (OD)		**Priming volume**	**Maximum Flow (L/min), *Q***						
		To avoid hemolysis (ml/M)	**Pressure gradient, Δ*P***		**Reynolds' number**		**Velocity, V**		
Inch	**Mm**			**< 5 mm Hg/m**	**< 10 mm Hg/m**	**<1,000 Laminar**	**< 2,000 Turbulent**	**<100 cm/s**	**< 200 cm/s**
3/16	4.5	15	<0.1	0.1	0.2	1.8	4.0	1.0	2.0
1/4	6	30	0.11	0.5	0.9	2.1	4.5	1.7	3.4
3/8	9	65	0.35	2.0	4.0	3.7	6.5	3.9	>6
1/2	12	115	0.45	3.8	7.0	5.0	9.5	>6	—
3/4	18	255	—	—	—	—	—	—	—

$\Delta P = (K_1 \, x \, N^2) - (K_2 \, x \, Q^2)$, where: K_1 and K_2 are constants of a particular pump, and N is a rotational speed. For an ideal pump K_2 is zero.



Typical relationship between total pressure head and flow rate for a centrifugal pump. N 1 through N 4 each represents a constant level of revolutions per minute (rpm), with N 1 representing the highest rpm value and N 4 the lowest.

Often to gain maximum benefit from the membrane oxygenator elimination of blood-gas interface, collapsible reservoirs are used in these circuits. Membrane oxygenators do require additional time to debubble (de-air). This may be facilitated by filling the circuit with carbon dioxide before priming with fluid, since CO_2 is considerably more soluble than oxygen and nitrogen. Oxygenators require a gas supply system. This requires at least a source of oxygen (but usually also air, and sometimes carbon dioxide), flow regulators, and flow meters. Often, when oxygen and air are used, a blender is used.

An oxygen analyzer should be incorporated in the circuit (after the blender, if one is used) as well as a microfilter. One or more anesthetic vaporizers are usually incorporated in the gas supply line to the oxygenator. Volatile anesthetic liquids may be destructive to the plastic components of extracorporeal circuits and, hence, one must consider the location of these vaporizers and use extreme care when filling them with anesthetic liquid so as to not 'contaminate' any plastic (including tubing) component.

Membrane oxygenators (Figure 10) are becoming the most preferred oxygenators for CPB. True membrane oxygenators do not allow the blood to come into contact with gases (in a manner equivalent to the natural lung). In this situation, the diffusion of gasses must occur through the membrane material. However, most modern membrane oxygenators do not have a complete barrier between the blood and gas. Modern membrane oxygenators are microporous membranes. These microporous membranes normally prevent large amounts of fluid from traversing the micropores, but allow the diffusion of oxygen and carbon dioxide. Hollow fibers constructed with micropores will carry either the gas or in some cases carry the blood through the oxygenator.

The most common material used for this type of oxygenators is silicon. These devices have wall thickness in the range of 50–200 microns. For a 130-micron thickness of silicon membrane, the permeability is about 215 mL (STP)/min*m^2 for oxygen and 1100 mL (STP)/min*m^2 for carbon dioxide (CO_2). The typical units of the thickness of normalized membrane gas permeability (P_m) are mL (STP) micron/min/m^2/atm. STP is an abbreviation of standard temperature and pressure conditions for the pure gas at 0˚C and 1 atm. The volumetric transport rate of a gas (N_v) can be obtained using Eq. (1).

$$N_v = (P_m * SA_m * (\Delta P_{gas}))/(T_m) \quad (1)$$

Where: P_m = Normalized membrane gas permeability, SA_m = Membrane surface area, ΔP_{gas} = Change in the gas partial pressure, and T_m = Membrane Thickness.

Recently, hollow-fiber systems employ hydrophobic microporous polypropylene membranes. Like the biological membrane, this artificial one allows for free passage of gas by diffusion through the membrane pores. However, since the pores are small, there is sufficient surface tension to prevent the plasma from filtrating. A column of air within the pores of these membranes has very high gas permeability when comparing to diffusion through the polymeric material itself. Furthermore, these membrane oxygenators have very high gas permeabilities.

There are many membrane based systems that come in various configurations: flat cross flow. The cross flow will typically have the gas plate, coil and hollow-fiber. The contact between the blood and gas can occur via concurrent, countercurrent, and flowing through the lumen of the hollow fiber, while tension to prevent plasma from filtrating. The size of such pores is in the order of 1 micron in diameter. Blood flows

across the outer surface of the fibers (3:169). Bubble oxygenators are simple in design and allow oxygen bubbles to move through the blood. Smaller bubbles are more efficient because of their higher surface area to volume ratio. But, smaller bubbles have a better chance of getting returned to the patient, because air bubbles are more difficult to remove from the blood. When bubble oxygenator are employed, gas flow must be initiated before the oxygenator is primed and continued thereafter to avoid leakage of fluid through the bubble disperser plate, which may degrade its efficiency (21:1). The bubbles in a bubble oxygenator produce high sheer stresses. This may be the cause of the bubble oxygenator's higher occurrence of hemolysis when compared to membrane oxygenator (3:55).

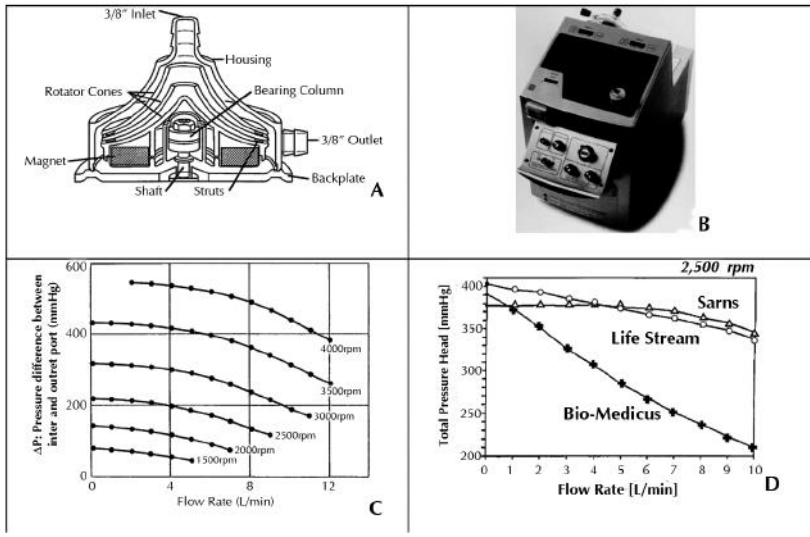


FIGURE 8 A. Cross sectional schematic of the BioMedicus Bio-Pump centrifugal pump; **B.** Console that drives and regulates the pump. Part of the pump mounted at the top rear of console; **C.** Hydraulic performance curves for the Bio-Pump; D. Hydraulic performance curves of BioMedicus, Life-Steam and Sarns pumps (Courtesy: Medtronic BioMedicus, Inc., Eden Prairie – MN).

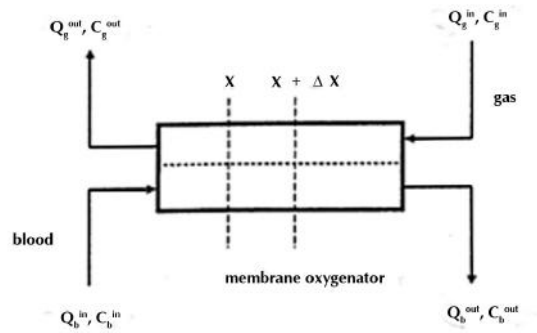


FIGURE 9 Membrane oxygenator.

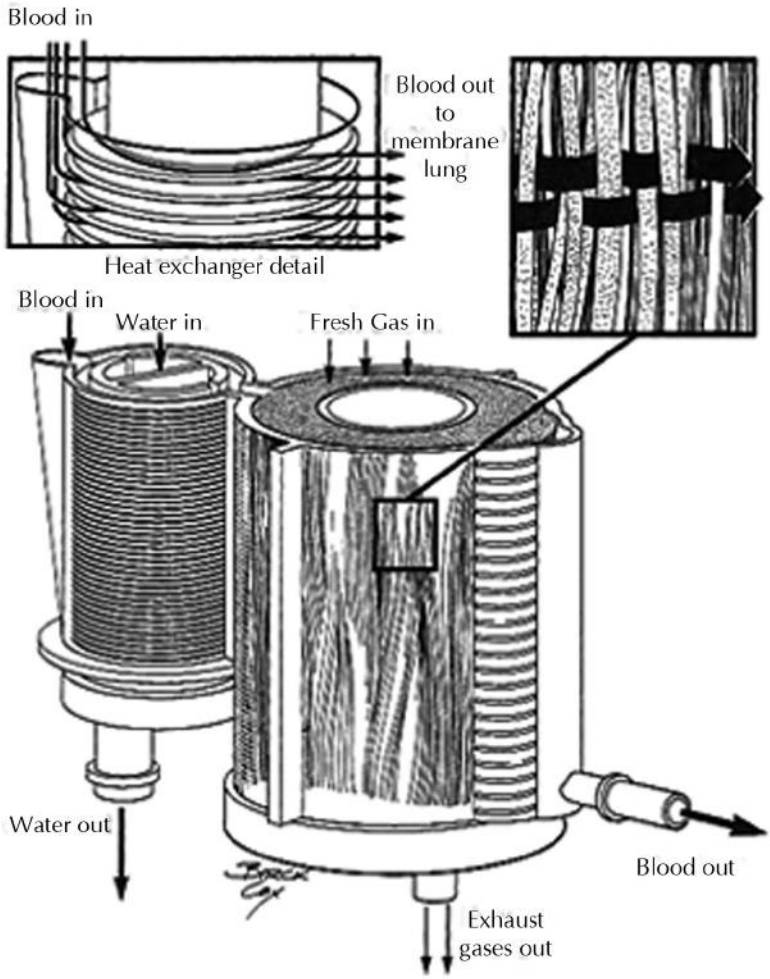


FIGURE 10 Membrane oxygenator with heat exchanger. Blood passes through the heat exchanger and then through the oxygenator.

2.4.5 CHARACTERISTICS OF OXYGENATORS

There are various characteristics between the human lungs and the blood pump oxygenators. It is understood that the artificial oxygenator will exemplify as closely as possible to the functions of the heart and lungs function. The blood oxygenation level must be equal, which implies is an excellent fluid for heat transfer, because it is simple, reliable and provides an even temperature distribution over surface of the heat exchanger. The surface material for heat transfer should have good thermal conductivity. Coated stainless steel and aluminum are common surface materials in heat exchangers. Figure 11 is an expanded circuitry of the CPB. Table 2 indicates operational characteristics of lungs and blood pump oxygenators.

2.5 PRIMING AND CONDITIONING

Prior to the introduction of CPB, topical hypothermia was used to arrest the heart during surgery. However, this proved unreliable because of the attendant risks of ventricular fibrillation and the relatively short period of time during which surgery could be performed without having irreversible cerebral anoxia. Today in most surgeries, hypothermia is used together with CPB (20, 185). The patient is placed under general anesthesia, during CPB. Early bypass systems were primed with whole blood. Nowadays, IV solution consists of a balanced electrolyte solution with near-normal ph and an ionic content similar to that of plasma. The priming solution removes all the air in the circuit, oxygenator and filter, and makes it bubble free. The priming solution is a mixture of donor blood and a type of saline solution. Saline solutions may be classified into crystalloids and colloids. Patients are often given both crystalloid and colloid solutions (Table 3).

To emphasize in the right doses of solution to be given, the consequences of under correction of fluid loss can lead to hypovolaemia, or if overcorrected can lead to pulmonary oedema and heart failure. Therefore, it is always best to insert a central venous pressure catheter to measure the central venous (right atrial) pressure.

2.6 PHYSICAL PROPERTIES OF BLOOD

Blood is a fluid connective tissue with a matrix called plasma that contains formed elements that float in this solution. Blood consists of about 46–63 % plasma and 37–54 % formed elements. Plasma is 92% water, 7% proteins and 1% of other solutes. Plasma proteins are 60% albumins, 35% globulins, 4% fibrinogen, and < 1% regulatory proteins. The other one percent of solutes is conformed by electrolytes (Na^+, K^-, Ca^+, Mg^+, Cl^-, HCO_3^-, HPO_4^-, SO_4^-), organic nutrients such as glucose, lipids, amino acids, etc., and organic wastes. Formed elements are divided as 99.9% RBC and 0.1% platelets and WBC. RBC provides oxygenation and ventilation, while WBC provide immune defense. Platelets are coagulants (7; 21). The physical properties of blood are shown in Table 4.

2.7 BLOOD SUBSTITUTES

Oxygen-carrying solutions take the role of RBC. Replacement of lost human blood with an oxygen-bearing substitute is essential for extreme blood loss. There is a process called antigen camouflage (still being tested). The process involves coating the RBC with a biocompatible polymer called polyethylene glycol (PEG). The PEG molecules form permanent covalent bonds on the surface of the cell. This coating effectively hides the antigenic molecules on the surface of the RBC so that the foreign cells are not recognized by the Blood recipient's antibodies. For example, a person who has type A Blood will naturally have antibodies that attach to the antigens on the surface of type B Blood cells and destroy the foreign Blood. The attachment of PEG to the surface of type B Blood camouflages the surface of the cell so the antigens can no longer be recognized and thus would prevent the destruction of the antigenically foreign RBC.

Another process of artificial perfusing is one that uses perfluorocarbons. Blood gases such as oxygen and carbon dioxide are highly soluble in perfluorocarbons, pharmaceutical products like Oxygent and Oxycyte, to name a few, are intended to provide an effective means of transporting oxygen to tissues and carbon dioxide to the lungs. Compared with hemoglobin, Oxycyte has been found to be capable of carryingat least five times more oxygen. Additionally, perfluorocarbons are considered to be more effective than hemoglobin for delivering oxygen at the tissue level. Efforts to develop a viable Blood substitute have thus focused on creating a hemoglobin alternative that can be stored for a long period of time at room temperature and can be transfused to restore the oxygen-carrying.

Function of hemoglobin without the need for type matching. By the beginning of 1999, four different hemoglobin-based oxygen carriers (HBOCs), developed by four separate companies, had entered the late stages of clinical development. Hemopure is a bovine-derived HBOC product.

Results show that the product can eliminate the need for allogeneic RBC transfusions in a significant number of patients undergoing vascular surgery. Hemopure has been administered to more than 600 patients in 21 completed or ongoing clinical trials. One unit of Hemopure contains 30 g of ultrapurified, chemically cross-linked hemoglobin in 250 mL of a balanced salt solution. When infused, this linked hemoglobin circulates in the plasma, and has a lower viscosity and it releases oxygen to tissues better than blood. Hemopure has been shown to be stable at room temperature for at least 30 months (15:1).

2.7.1 PLATELETS SUBSTITUTION

Among the products being considered acting as a replacement for human Blood platelets, specifically to treat thrombocytopenia are ‘Synthocytes’ and are being developed by a British company. Synthocytes are microcapsules to which fibrinogen has been chemically linked. The Synthocytes are capable of selectively targeting the site of hemorrhage, according to the company. The product is believed to offer certain key advantages over Blood-derived platelets, that have the potential to transmit viral infections, suffer from instability during storage, and cause immune reactions.

2.7.2 ANTICOAGULANTS

Heparin is made from bovine lung tissue or porcine intestinal mucosa. This substance prevents the formation of blood clots by producing a conformational change in antithrombin III and converting it to a rapid inhibitor or factor V and factor VIII (9:187). Heparin is given before cannulation for CPB or prior to clamping blood vessels. The dose for a patient weighing 70 kg is about 21000 units or 210 mg. To determine whether the blood is appropriately heparinized, the activating clotting time (ACT) is measured after three minutes of infusion but before CPB is initiated. Occasionally adequate anticoagulation is difficult to achieve but increasing the dose will usually suffice. Protamine sulfate would come to be the antidote of heparin in the presence of it but if not present it acts as an anticoagulant. Protamine sulfate would be administered when the operation is about to conclude and a quantity of 1 to 1.3 doses of heparin would be sufficient.

TABLE 2 Operational characteristics of lungs and blood pump oxygenators.

Characteristics	Units	Lungs	Oxygenators
Blood flow rate	L/min	5	5
Pressure head	mm Hg	12	0–200
Blood volume	L	1	1–4
Blood film thickness	μ	510	100–300
Length of blood flow channel	–	100 μ	2–30 cm
Blood contact time	s	0.7	3–30
Surface area for mass transfer	m^2	70	2–10
Gas flow rate	L/min	7	2–10
Blood in: PO_2/PCO_2	mm Hg	40/45	40/45
Blood out: PO_2/PCO_2	mm Hg	95/40	100–300/30–40
Gas in: PO_2/PCO_2	mm Hg	149/0.3	250–713/0–20
Gas out: PO_2/PCO_2	mm Hg	120/27	150–675/10–30
PO_2 gradient	mm Hg	40–50	1.52
PCO_2 gradient	mm Hg	3–5	30–50

TABLE 3 Common IV solutions. All ions are in mEq/L.

Solution	Glucose (g/L)	Na^+	K^+	Ca^{+2}	Cl^-	Lactate	PO_{4-}^{3}	Mg^{+2}
5% Dextrose (D_5W)	50	0	0	0	0	0	0	0
10 % Dextrose ($D_{10}W$)	100	0	0	0	0	0	0	0
Normal saline (NS)	0	154	0	0	154	0	0	0
D_5NS	50	154	0	0	154	0	0	0
$D5^{1/2}NS$	50	77	0	0	77	0	0	0
0.2%NS	0	31	0	0	31	0	0	0
3%NaCI	0	513	0	0	513	0	0	0
Ringer' Lactate (LR)	0	130	4	3	109	28	0	0
D^5LR	50	130	4	3	109	28	0	0
$D^{10}E\#48$	100	30	15	0	20	25	3	3
$D^5E\#48$	50	25	20	0	22	23	3	3
$D^{10}E\#75$	100	57	35	0	40	25	12	6
$D^6E\#75$	60	40	40	0	35	20	15	0

Other additives to the prime may include albumin or hetastarch (to raise the plasma colloidal oncotic pressure), diuretics such as Mannitol and Furosemide (to draw fluid from the interstitial space into the vascular space), and vasodilators (to counteract the vasoconstriction produced by catecholamines). Steroids may also be added to improve tissue perfusion and lessen the increases in extracellular water. Vasodilators are used more in pediatrics or neonatals, i.e., chlorpromazine, Et-1. Systemic inflammatory response in patients undergoing CPB can be reduced to a certain level with sodium nitroprusside, and the activation of vascular endothelial cells can be inhibited. The myocardium is protected against ischemia/reperfusion injury in cardiac surgery and cardiology through the use of cardioprotective shock proteins (Hsp), in particular Hsp 70.

2.7.3 POSTOPERATIVE DRUGS

Nitric oxide decreases platelet loss, platelet damage, postoperative bleeding, and lessens the need for postoperative blood transfusions (24,1C2). Thyroid hormone has important effects on the heart and peripheral vascular system, specifically triiodothyronine (T3).

Data suggests that T3 repletion may improve postoperative hemodynamic performance and lower the incidence of arrhythmias. Diltiazem is used in patients who have mild-to-moderate renal dysfunction and undergo cardiac surgery using cardiopulmonary bypass (24:1). To reduce bleeding during and after CPB, drugs and their respective dosage are: (1) Aprotinin (Trasylolâ) – 200 mL at induction, 200 mL on the pump, and 50 mL/hr for 24 hr. (2) Aminocaproic Acid (Amicarâ) – 5 gm at induction, 5 gm on the pump, and 1 gm/hr or 5 hr. (3) Tranexamic Acid (Cyklokapronâ) – 10 gm IV at induction followed by postop1 gm/hr for 5 hr.

2.8 BIOFLUID DYNAMICS

The CPB delivers O_2 and carry away CO_2 (5:9C3). Let us consider how these molecules move across membranes. Unlike most biologically important molecules, O_2 and CO_2 do not have specific membrane transport systems. They must pass directly through membranes by diffusion (1:4).

2.8.1 DIFFUSION

Diffusion is the random movement of molecules due to thermal energy. The net movement of a group of molecules will be from an area of high concentration to an area of low concentration, along a concentration gradient (2:4). In media such as water or air, diffusion is extremely inefficient because of constant collisions with other molecules. A diffusing O_2 molecule is, in essence, involved in a walk that involves constant, random turns. The time (t) required to move a distance (x) by a diffusing molecule can be described by the following equation (5:1):

$$t \approx \frac{x^2}{2D} \tag{2}$$

Where: D = the diffusion coefficient. A molecule moving twice as far as another will take four times longer. According to this equation, a small particle will move a distance

of 1 μm (the width of a bacterium) in 0.5 m-sec. In order to travel across a test tube (1 cm) the same particle would take around 14 hr (for a small molecule in water, at room temperature and at D » 10^{-5} cm^2/sec). Obviously, diffusion over a long distance will not work for an organism with a rapid, demanding metabolism. The primary purpose of the cardiopulmonary system is to overcome the limitations of diffusion. Diffusion is a crummy way to move molecules; however, it will work if the distances are small. The cardiopulmonary system delivers an oxygen rich solution very close to cells.

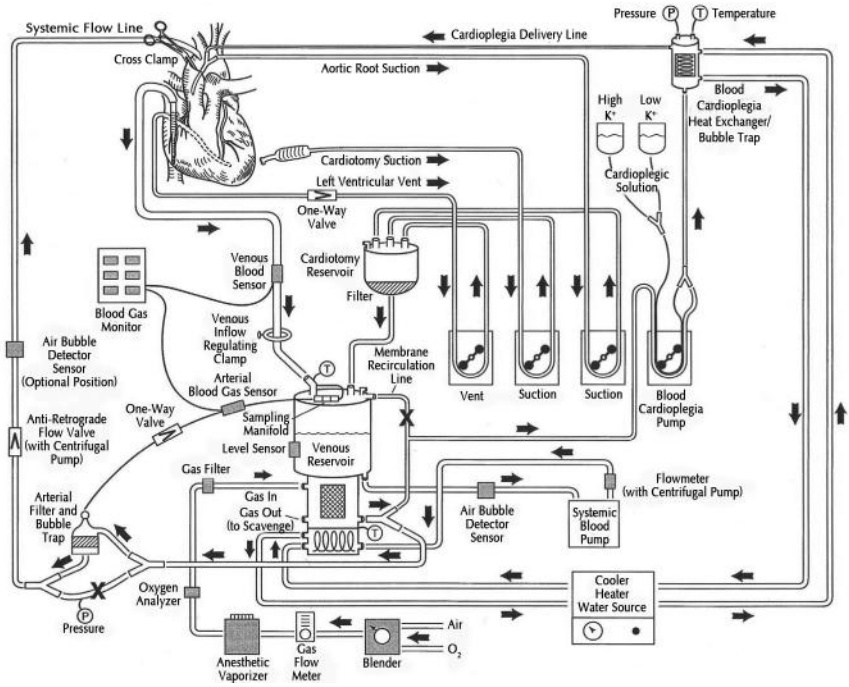


FIGURE 11 Extended circuit model of a cardiopulmonary bypass (CPB).

The result is that multicellular organisms can have organs several centimeters away from the atmosphere. In a functional sense these organs are only a few μm from the atmosphere. **Fick's first law** relates the diffusive flux to the concentration under the assumption of steady state. The flux goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the concentration gradient (spatial derivative). Fick's first Law for one dimension is defined in Eq. (3):

$$J = DA\frac{dc}{dx} \backslash^* \text{ mergeformat} \tag{3}$$

Where: J is a diffusion flux and measures the amount of substance that will flow through a small area during a small time interval ((amount of substance) per unit area per unit time); D is the diffusion coefficient or diffusivity in dimensions of ($length^2$ $time^{-1}$); A is the area, c is the concentration in dimensions of ((amount of substance)

TABLE 4 Physical properties of blood.

Property	Remarks	Units Normal	Value		Comments
			Range		
WHOLE BLOOD					
Dielectric constant	—	—	8.25	8.0–8.5	—
Freezing point depression	30	°C	0.567	0.557–0.577	—
pH	2–3 yr	—	7.35	—	Arterial blood
	3–18 yr	—	—	7.38–7.40	Arterial blood
	—	—	7.31	—	Venous blood
	50–70 yr	—	—	7.35–7.40	—
Refractive index	30	—	17.4	16.2–18.5	—
Refractive viscosity at 20°C	M	—	4.71	4.09–5.10	In vitro determination
	F	—	4.46	4.08–4.66	Hirudin anticoagulant
At 37°C	M	—	3.00	2.18–3.59	Oxalated blood in vitro determination
Specific gravity	F	—	1.058	1.052–1.064	Copper sulfate method no anticoagulant
	infant	—	1.064	1.056–1.075	Falling drop method
	M	—	1.056	1.050–1.062	
At 25/4°C	F		1.056	1.052–1.061	Copper sulfate method
Specific heat	—	g-cal	0.92	—	—
Surface tension	—	dynes/cm	—	(55.5–61.2)	—

TABLE 4 *(Continued)*

Property	Remarks	Units Normal	Value		Comments
			Range		
ERYTHROCYTES					
Electrical charge	M/F	10^4 electrostatic units	5.21	—	In M/15 phosphate buffer at pH 7.4
Electrophoretic mobility	—	x 10–^{4} cm^2/volt-s	1.31	—	In M/15 phosphate buffer at pH 7.4
ph	—	—	7.396		—
Specific gravity	—	—	1.0989	1.0942–1.1069	Gravimetric method
	F	—	1.0932	1.089–1.097	Not corrected for an estimated 7% trapped plasma copper sulfate method
At 25/4°C					
	—	—	1.098	1.095–1.101	Corrected for trapped plasma; copper sulfate method
Specific heat		g-cal	0.77	—	—
PLASMA OR SERUM					
Colloid osmotic pressure		mm H_2O	330	280–480	—
	Fasting	mm H_2O	344	310–376	Arterial blood
		mm H_2O	337	300–373	Venous blood
Electrical conductivity	20°C	× 10^4 mho	106	105–111	—
	25°C	× 10^4 mho	120	117–124	—
Freezing point depression	30 M, 20 F	°C	0.532	0.512–0.552	Vapor pressure method
	21	°C	0.537	0.515–0.559	Vapor pressure method
	28 M	°C	0.534	0.521–0.547	Vapor pressure method
	44 M, 31 F	°C	0.540	0.512–0.568	Beckmann thermometer method
	22 M,17 F	°C	0.536	0.524–0.568	Fiske osmometer method

TABLE 4 *(Continued)*

Property	Remarks	Units Normal	Value		Comments
			Range		
Isoelectric point pH	M	—	5.5	—	—
	F	—	6.0	—	—
pH	—	—	—	7.30–7.40	—
Refractive index	—	—	17.1	16.0–18.2	At 17.5°C
	—	—	—	1.349–1.351	Abbe refracto meter method
Relative viscosity	—	—	1.86	1.80–1.95	In vitro determination
	13–22° C	—	1.89	1.75–2.05	Herudin anticoagulant
	14–23° C	—	1.32	1.18–1.59	Plasma from oxalated blood; in vitro
	37° C	—	1.22	1.11–1.41	In vitro determination
Specific gravity	M	—	1.027	1.024–1.030	Copper sulfate method; no anticoagulant
	M/F	—	1.027	1.024–1.030	Falling drop method
at 25/4°C	—	—	1.028	1.026–1.031	Gravimetric method
	F	—	1.024	1.022–1.026	Copper sulfate method
Specific heat	—	g-cal	0.94	—	—
Surface tension	Child	dynes/cm	52	42–62	—
	ó	dynes/cm	75.1	—	—
		dynes/cm	69.9	—	—

length^{-3}); and is concentration and x is the position, dc/dx represents the concentration gradient. This equation gives us some insight into the cardiopulmonary physiology system and gas exchange. In two or more dimensions we must use the del or gradient operator.

2.8.1.1 DIFFUSION COEFFICIENT

In order to maximize diffusion we must have a large diffusion coefficient or, in other words, very thin, permeable membranes at the exchange surfaces. The endothelial cells of capillaries (i.e. the capillary wall) are extremely thin. Indeed, on a light microscope it is difficult to see the thin cytoplasmic extensions of these cells; they can be easily visualized only where the nucleus creates a bulge. Likewise, at the pulmonary surface, the combined alveolo capillary membrane is quite thin (0.2–0.6 micrometers) and presents only a small diffusion barrier during normal (healthy) conditions. There is, however, a 'down-side' to highly permeable membranes. Since these membranes are so thin and permeable they are highly susceptible to damage and are a favorite point of entry for pathogens.

2.8.1.2 AREA

A large area must be present at both the atmospheric interface and at the body tissue level in order to have a large rate of diffusion. It is estimated that the lungs have 300 million alveoli with a combined surface of around 160 m^2. In the body tissues, there are 10 billion capillaries having a total surface area of hundreds of square meters (the estimates vary from 500 m^2 to 6,000 m^2). To put these numbers in perspective consider the following: The alveolar surface area is about the same as that of a tennis court. At any given time, the lungs contain about 100 mL of blood. Imagine spreading 100 mL of water (about a half cup) evenly over a tennis court. This should give us some idea of the diffusion distances involved and why gas exchange is so incredibly efficient in the lungs. The rate of diffusion is to have a large concentration gradient. As molecules diffuse they tend to evenly disperse and reach an equilibrium concentration and, at this point, net diffusion stops (2, 5, 8). In the circulatory system, equilibration is prevented by the constant movement of blood. In effect, the moving blood continuously refreshes the concentration gradient.

2.8.1.3 CONCENTRATION GRADIENT

A third way of assuring high oxygen consumption, the concentration gradient decreases and the tissues become deficient in oxygen.

2.8.2 PRELIMINARY MODEL OF THE CARDIOPULMONARY SYSTEM

Using Fick's Law, a model for a cardiopulmonary system is shown in Figure 12. In order to move blood, we need a pump and plumbing (5:9). This diagram is actually a fairly good representation of the cardiopulmonary (CB) system.

2.8.2.1 EXPANDED MODEL OF THE CARDIOPULMONARY SYSTEM

In Figure 13, the two pumps (i.e., left and right heart) are fused into one (1, 2, 4, 8:1). The left heart feeds the systemic circulation with a relatively high-pressure head and contains the great majority of the blood. Because of the larger volume of blood that is supplied, this side of the circuit is sometimes called the greater circulation. The right heart pumps into pulmonary circulation (sometimes called the lesser circulation), which has about one fifth the pressure head and holds about 12% of the blood volume compared to systemic circulation. Although pump sizes are different, rate of blood flow is the same in the systemic and pulmonary circulations.

2.8.3 TRANSPORT PROCESSES

Mathematical modeling of the CPB is similar to models representing hemodialysis in addition to the binding of oxygen onto hemoglobin. A mass balance law (Continuity equation) is considered to model the CPB. It states that the total flow rates are unchanged. Assume C_b and C_g are the bulk concentrations of the blood (b) and gas (g). C'_b is an amount of oxygen in the blood that is bound to hemoglobin while C_{bm} and C_{gm} are the corresponding concentration values at the membrane surface on the blood and gas sides. Considering this notation, a mass balance (Eq. (4)) for a membrane length of Δx can be written on the presence of O_2 on both sides, blood and gas.

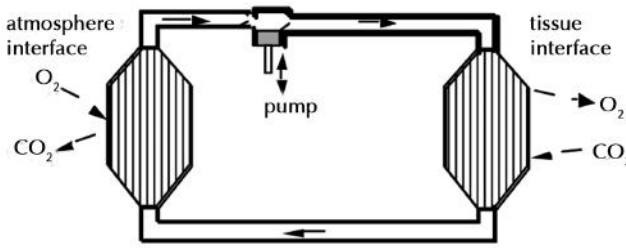


FIGURE 12 Cardiopulmonary system model.

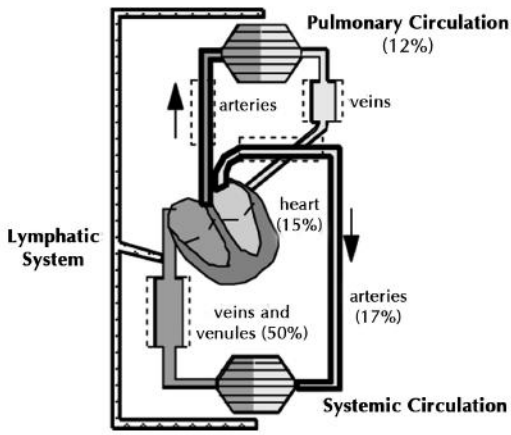


FIGURE 13 Expanded Model of CB System (numbers indicate the percent of blood volume in different portions of the circulation).

$$Q_b(C_b + C'_b)\big|_x - Q_b(C_b + C'_b)\big|_{x+\Delta x} = k_b W_b \Delta x (C_b - C_{bm})$$
$$Q_g C_g\big|_{x+\Delta x} - Q_b C_g\big|_x = k_g W_g \Delta x (C_g - C_{gm}) \quad (4)$$

$$Q_b \frac{d(C_b + C_b^{'})}{dx} = -k_b W_b (C_b - C_{bm}) \quad (5)$$

$$Q_b (1+m) \frac{dC_b}{dx} = -k_b W_b (C_b - C_{bm}) \quad (6)$$

$$Q_b (1+m) \frac{dpO_{2b}}{dx} = -k_b W_b (pO_{2b} - pO_{2bm}) \quad (7)$$

$$Q_g \frac{dpO_{2g}}{dx} = -k_b W_b (pO_{2g} - pO2_{gm}) \quad (8)$$

$$\frac{1}{K_o} = \frac{H}{k_b} + \frac{W_b}{\rho^{STP} P_m W_L} + \frac{RTW_b}{k_g W_g} \quad (9)$$

$$\frac{Q_b (1+m)}{H} \frac{dpO_{2b}}{dx} = -k_b W_b (pO_{2b} - pO_{2bm}) \quad (10)$$

$$\frac{Q_g}{RT} \frac{dpO_{2g}}{dx} = K_o W_b (pO_{2g} - pO_{2b}) \quad (11)$$

$$pO_{2g}(x) = \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right)(1+m)\left[pO_{2b}(x) - pO_{2b}^{in}\right] + pO_{2g}^{out} \quad (12)$$

$$\frac{dpO_{2b}}{dx} = \left(\frac{K_o W_b H}{Q_b (1+m)}\right)\left\{\begin{array}{l}\left[\left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right)(1+m) - 1\right] pO_{2b} \\ + \left[pO_{2g}^{out} - \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right)(1+m)\, pO_{2b}^{in}\right]\end{array}\right\} \quad (13)$$

$$A_{oxygen} = \frac{\alpha}{\beta} \ln\left(\frac{\beta pO_{2b}^{out} + \gamma}{\beta pO_{2b}^{in} + \gamma}\right) \quad (14)$$

$$\alpha = \frac{Q_b(1+m)}{K_o H}$$

$$\beta = \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right)(1+m) - 1 \tag{15}$$

$$\gamma = pO_{2g}^{out} - \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right)(1+m)\,pO_{2b}^{in}$$

In the above equations, k_b and k_g are the coefficients mass transfer for blood and gas side. W is the membrane area per unit length of membrane, for either the blood (*b*) or the gas (*g*) side. This applies for the cylindrical membranes. However, in planar membranes, $W = W_b = W_g$. After rearranging Eq. (4) and dividing by Δx, we get Eq. (5). Knowing that this is the slope of the oxygen-dissociation curve, it can be assumed constant and evaluated at some suitable combination of the venous and arterial PO_2 values, the blood-side to yield Eq. (7). Now, we can include the concentration of the partial pressure in the mass-transfer description process. Apply Henry's Law, $PO_{2b} = HC_b$ ($H = 0.74$ mm Hg/μM), and the ideal gas law for the gas side, $PO_{2\,g} = RTC_g$, we get Eq. (8). Rewriting Eq. (8) with the overall partial pressure as the driving force, ($O_{2\,g}$-pO_{2b}), we get Eq. (9). ρ^{STP} represents the density of the gas at STP conditions. KO is based on the membrane area on the blood side. Further simplification gives Eqs. (10) and (11). Equation (11) may be integrated from the entrance of the blood stream, $x = 0$, to any arbitrary value of to give Eq. (12). Substituting Eq. (12) into (10), we get Eq. (13).

Integrating for the blood will in the housing, we get Eq. (14) for the blood-side membrane area.

In the membrane oxygenator analysis, we should consider the carbon dioxide transfer. The reader may note that carbon dioxide is present in the blood in many forms, such as, dissolved gas, combined with H_2O, hemoglobin, and other proteins. Just as the oxygen, the total amount of carbon dioxide present depends on its partial pressure. There is about 50 mL of carbon dioxide at BTP in each 100 mL of blood at a PCO_2 of about 42 mm Hg.

The change in concentration of this gas in the human body is very low. For instance, the venous blood has about 45 mm Hg in PCO_2 which correspond to 52% volume while the arterial blood has approximately 40 mm Hg PCO_2 corresponding to a concentration of 48 percent volume. Knowing this, Henry's constant for carbon dioxide can be obtained which is in the range of approximately 0.0022 mm Hg/μM. It is assumed that Henry's law describes the relationship between the concentration and the partial pressure of the gas. Here we have the overall mass-transfer coefficient, KO, recognizing that CO_2 should be used in this transport mechanism of the oxygenators to yield Eqs. (16) and (17). The Eq. (18) is just as for oxygen, subtracting the gas-side from the blood-side; and integrating to provide the relationship between $PCO_{2\,g}$ and $PCO_{2b.}$ The differential Eq. (19) for PCO_{2b} is obtained by substituting 18/in Eq. (16).

By integrating the Eq. (19) over the total length of the oxygenator, we get Eq. (20) for the blood-side membrane surface area needed to remove the carbon dioxide. In Eqs. (14) and (21), the constants, α,' β,' have the same units.

$$\frac{Q_g}{RT}\frac{dpCO_{2g}}{dx} = K_o W_b (pCO_{2g} - pCO_{2b}) \tag{16}$$

$$\frac{Q_b}{H}\frac{dpCO_{2b}}{dx} = K_o W_b (pCO_{2g} - pCO_{2b}) \tag{17}$$

$$pCO9(x) = (\frac{Q_b}{Q_g})(\frac{RT}{H})[pCO_{2b}(x) - pCO_{2b}^{in}] + pCO_{2g}^{out} \tag{18}$$

$$\frac{dpCO_{2b}}{dx} = \left(\frac{K_o W_b H}{Q_b}\right)\left\{\begin{array}{l}\left[\left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right) - 1\right] pCO_{2b} \\ + \left[pCO_{2g}^{out} - \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right) pCO_{2b}^{in}\right]\end{array}\right\} \tag{19}$$

$$A_{carbondioxide} = \frac{\alpha'}{\beta'} \ln\left(\frac{\beta' pCO_{2b}^{out} + \gamma'}{\beta' pCO_{2b}^{in} + \gamma'}\right) \tag{20}$$

$$\begin{aligned} \alpha' &= \frac{Q_b}{K_o H} \\ \beta' &= \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right) - 1 \\ \gamma' &= pCO_{2g}^{out} - \left(\frac{Q_b}{Q_g}\right)\left(\frac{RT}{H}\right) pCO_{2b}^{in} \end{aligned} \tag{21}$$

When using a CPB system, it is important to consider: Effects of temperature on the viscosity of blood with varying hematocrit levels (Figure 14); and the positive and negative effects of the system in a patient. All clinical and technological outcomes should be addressed and considered.

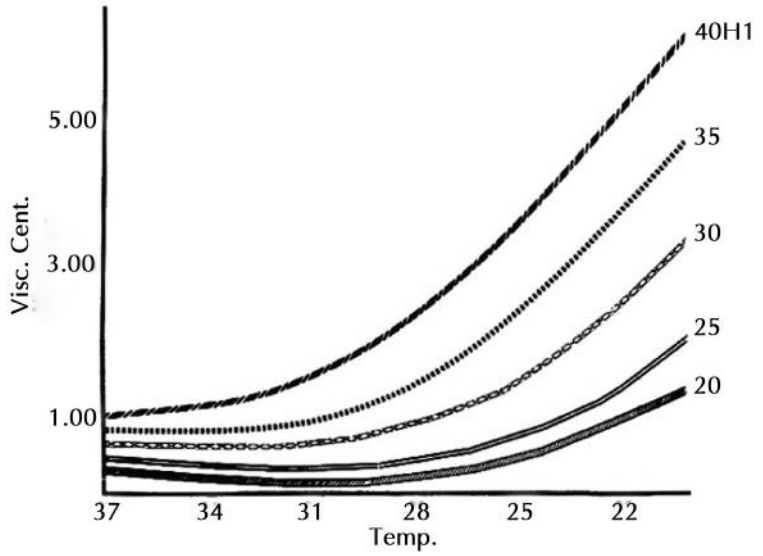


FIGURE 14 Effects of temperature on the viscosity of blood with varying hematocrit levels (4:562).

2.8.4 MONITORING AND SAFETY PROCEDURES

The monitoring of the factors in CPB is important for maintaining adequate perfusion and organ system viability. A perfusionist must continuously monitor: systemic blood flow, venous blood drainage, gas composition, gas flow rate, and blood temperature. Other factors monitored are: blood pressure, electrocardiogram (ECG), electroencephalogram (EEG), urine flow, and coagulation status. Constant monitoring can help the CPB team to anticipate any unfavorable conditions and take appropriate action.

An appropriate blood flow rate is important in CPB. If the flow rate is too fast, blood damage is more likely and the perfusionist's reaction time is less. If the flow rate is too slow, the patient will not acquire satisfactory levels of gas exchange. Blood flow is monitored with an electronic flow meter when a centrifugal pump is used. Venous blood drainage is monitored by continuously checking the volume of blood in the reservoir. If it is determined that the flow rate is undesirable, the perfutionist can adjust the pump's rotational speed.

Perfusion pressure is another factor that is constantly maintained throughout CPB. The total volume of fluids in the system has a direct relation on the pressure and crystalloid solution can be added into the circuit during CPB. The pressure is also influenced by the flow resistance of the blood. The flow resistance is primarily affected by the vasomotor tone (average diameter of arteries) and blood viscosity. The viscosity is affected by the temperature and by the extent to which the blood is diluted. The viscosity is decreased due to dilution with prime solution. However, the temperature of the blood is decreased during CPB to induce hypothermia. This decrease in temperature has the opposite effect on viscosity. Figure 14 shows the effects of temperature on the viscosity of blood with varying degrees of dilution. Vasoactive drugs can be used

to control the degree of relaxation and contraction of the blood vessels. Monitoring perfusion adequacy is accomplished by measuring hemoglobin oxygen saturation, pH and lactate concentration. Excessive oxygen consumption can be due to inadequate anesthesia or inadequate hypothermia.

Throughout CPB, pressures are also monitored in the pulmonary artery, left atrium, and veins. Elevated venous pressure can reduce the effective perfusion pressure for the brain, kidneys and abdominal viscera. Also, edema production is enhanced with a higher venous pressure. Another cardiovascular monitor in CPB is the electrocardiogram (ECG). Since the heart is to remain at rest during surgery, proper levels of cardioplegic solution and hypothermia must be maintained. If the ECG detects electrical activity in the heart, another infusion of cardioplegic solution may be necessary or the temperature adjusted. An electroencephalogram (EEG) is also used with measurements of neurological activity from the body surface to verify muscle paralysis. They are also monitored to detect functional abnormalities developing during the surgery. However, many physiologic changes during CPB such as hypoperfusion, hypoxia, hypothermia, anesthesia, systemic flow changes and pulsality changes can complicate the interpretation of the EEG.

The temperature is another important factor in CPB and is usually monitored at two or more locations of the body. Temperature monitoring is most important for the organs that are most vulnerable to hypoperfusion, such as the brain. The best way to estimate brain temperature is to measure the temperature of nasopharyngeal tissue, the tympanic membrane or the esophagus below tracheal bifurcation. During the rewarming of a patient, it is important to avoid the liberation of free gas bubbles. Gradual rewarming can generally prevent this from happening. It is recommended to maintain $<10°C$ difference between the heat exchanger and venous blood during rewarming.

Urine flow is constantly monitored throughout CPB. Although urine flow can indicate that the kidney is functioning properly during CPB, postoperative renal function is mainly affected by the amount of time on bypass and preexisting renal failure (4,568). The coagulation status of the blood is monitored by periodically testing the activated clotting time. This is usually done with a special device that uses a small amount of blood for the test. Heparin concentration levels can also be monitored, but this may be useless for patients that have a high resistance to heparin.

2.8.5 ADVERSE EFFECTS

Although CPB has made possible the repair of congenital and acquired cardiac disorders with relatively low morbidity and mortality, it is not a totally benign intervention. All patients respond physiologically to CPB to some degree (9:1). Significant adverse reactions can occur, especially in the very young and the very old producing what is called the "postperfusion syndrome." This is evidenced by prolonged pulmonary insufficiency, excessive accumulation of extravascular water, elevated temperature, vasoconstriction, coagulopathy, and variable degrees of renal and other organ dysfunction. The proposed mechanism for these damaging effects is the exposure of blood to the abnormal surfaces of the CPB circuit, as well as conditions such as hypothermia and altered blood flow, which initiate a systemic inflammatory response. This inflammatory response produces, releases, or alters a host of vasoactive substances that react

with specific receptor proteins throughout the body. The resulting vascular smooth muscle and endothelial cell contractions are responsible for many of the morbid complications associated with CPB.

2.9 TECHNOLOGY ADVANCES

Although CPB has been in long use in the cardiovascular surgeries, yet it is not as efficient as desired. At the moment, there are various concepts and experiments that are being investigated to improve its functionality and performance and some of these ideas are being implemented.

One of most interesting studies relates to a technique for CPB using a vacuum system for venous drainage with a pressure relief valve (11:1). As mentioned earlier, the venous drainage of cardiopulmonary bypass is driven by the pressure gradient between the central venous pressure and the pressure in the reservoir. Addition of a pressure release valve to the original design will provide a constant negative pressure when blood suction is used: it will decrease the circuit priming volume and consequently will reduce the degree of hemodilution. There is an increase in stability between the system and the patient, and a decrease in hemoglobin loss. This system is optimal especially for minimally invasive surgery.

The current oxygenators are efficient enough for short-term usage, for example, a cardiopulmonary bypass; however, there are certain disadvantages for the long-term usage (12:4). Porous membranes tend to cause vapor loss via micropores, causing serum leakage and eventual interference with gas transfer. Another study uses Heparin as coating to extend the durability of the oxygenators in cardiopulmonary bypass systems. It has been found that coating of the CPB system with heparin will result in a longer oxygenator service life. Coating the membrane may be a solution to prevent the leakage and heparin coating is the most practical way to do so. A recent study shows the advantages of this technique by comparing the durability of coated oxygenators with noncoated ones. The reasons for improved durability of the system due to heparin coating have not been clarified.

Efforts are being made to continue enhancing the durability of the cardiopulmonary bypass system and to increase stepwise multivariate proportional hazards regression analysis, as well as an increase in platelet count due to the fact that heparin coating increases biocompatibility with the blood and restores the platelets count.

Another interesting study is being conducted on a compact centrifugal pump and membrane oxygenator in place of the conventional (10:1). The conventional system is large and bulky, retaining a large volume of blood circuit which clinically, and it is a disadvantage for the health of a patient. This study has revealed that the compact system decreased blood trauma, activation of blood coagulation parameters, the maximum plasma free hemoglobin, activation of thrombin production consequently, beneficial for the patient.

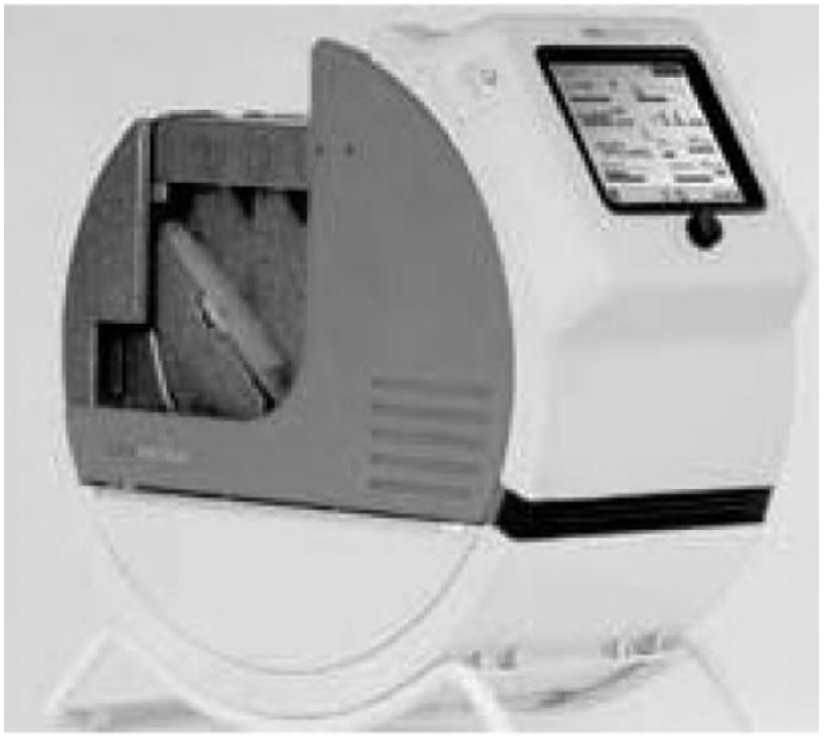


FIGURE 15 The compact 17.5 kg heart-lung machine Lifebridge B2T. <http://illumin.usc.edu/printer (14) engineering-the-heart-lung-machine/>

2.9.1 HEART-LUNG MACHINE OF THE FUTURE

There are dozens of heart-lung machines currently on the market today that are widely used across the nation. Most of these machines employ the same basic components and functions. However, like most areas of science and engineering, the technology of the heart-lung machine is dynamic. Recent breakthroughs of biomedical engineers give a glimpse of the cardiopulmonary bypass machines of the future. In 2007, the world's first portable heart-lung machine received the CE mark, which officially allowed it to be sold across Europe. Weighing only 17.5 kilograms and powered by a rechargeable battery, the Lifebridge B2T can be transported to different parts of a hospital, giving paramedics or emergency room physicians the chance to start extracorporeal circulation in critical patients before even reaching the operating room (Figure 15, "Ready for action: The 17.5 kg heart-lung machine. European Hospital Online: http://www.european-hospital.com/topics/article/2412.html").

Another new development of the heart-lung machine is a miniaturized heart-lung machine (MiniHLM) developed for infants. Instead of having all the components spaced separately, as with normal-sized machines, the MiniHLM integrates the functions so

the machine is much smaller and more compact. This allows cardiac bypass surgery to be performed on neonates, something that will surely expand the capacity with which heart conditions in newborns can be treated. For more details, the reader may consult: "*J. H. Schnöring-Arens, F. Reisch, J.F.* Vázque*z-Jiménez, T. Schmitz-Rode, and U. Steinseifer, 2008. Development of a miniaturized heart-lung machine for neonates with congenital heart defect. American Society for Artificial Internal Organs Journal, 54(5):509–13. Weblink: http://www.ncbi.nlm.nih.gov/pubmed/18812743?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum, 2008."*

Current implementations of the cardiopulmonary bypass machine have advanced far past John Gibbon's original idea. Yet no step in the process has been insignificant, as every improvement has improved the safety and usability of the machine. Engineers continue to consider both the biological needs of the human body and the basic principles of physics in order to create a functional biocompatible device that performs what was once unthinkable, sustaining human life without the use of one's heart or lungs. Hundreds of thousands of patients undergo open-heart bypass surgeries every year, intense procedures which require extracorporeal circulation. That's hundreds of thousands of lives saved with the help of one essential biomedical device: the heart-lung machine (AHA Open-Heart Surgery Statistics. American Heart Association: http://www.americanheart.org/presenter.jhtml?identifier=4674, 2009).

2.10 SUMMARY

The idea that blood could be infused into organs to maintain their viability had been suggested in the early part of the nineteenth century. However, throughout the years, the heart – lung machine could not have become a reality without the work of researchers whose discoveries provided the theoretic and scientific basis for extracorporeal circulation. There have been several different types of pumps as well as types of oxygenators for this application. The cardiovascular surgery itself is a difficult procedure. However, when the CPB system is involved, the procedure seems to become more complex, involving mechanical, physiological and environmental factors. The main function of the system is to oxygenate the blood and pump it back to the rest of the body. Even though, some of these parameters are still difficult to match, the functionality of the CPB is merely close to the physiological behavior. Still, technology is always increasing specially in the biomedical industry. Therefore, new techniques and implementations have already been designed in order to increase the performance and efficiency of the CPB.

Cardiopulmonary bypass (CPB) is needed when the natural function of the heart and lungs must be stopped during the heart surgery. A thorough explanation of CPB's procedures, components and fluid mechanics of the system are presented in this chapter.

KEYWORDS

- **Blood substitute**
- **Blood thinner**
- **Blood**
- **Blood filters**
- **Bubble oxygenator**
- **Cannula**
- **Cardioplegia infusion**
- **Cardiopulmonary bypass surgery**
- **Cardiotomy suction**
- **Catheter**
- **Centrifugal pump**
- **CPB**
- **Diffusion**
- **Heat exchanger**
- **Hemodilution**
- **Hemostasis**
- **Heparin**
- **Hypothermia**
- **Intracardiac vent**
- **Intravenous fluid**
- **IV fluid**
- **Membrane oxygenator**
- **Morbidity**
- **Oxygenation**
- **Oxygenator**
- **Percutaneous**
- **Perfusion**
- **Pulsatile pump**
- **Roller pump**
- **Spallation**
- **Sternotomy**
- **Thrombus**
- **Venous reservoir**

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CHAPTER 3

BIOMECHANICS OF ARTIFICIAL HEART[1,2]

CONTENTS

[1] This chapter has been modified from the review article that was prepared by my students (Sachin Gursahani, Eric Ponce, Mahesh Nagaraju and Sujit Tatke) for the course on Biofluid Mechanics, BME 4994. Course Instructor: Megh R. Goyal, PhD, PE, Visiting Professor in Biomedical Engineering (2003), Biomedical Engineering Department, Florida International University, 10555 West Flagler Street, Miami – FL 33174, USA. For details contact at <goyalmegh@gmail.com> or visit: http://www.ece.uprm.edu/~m_goyal/home.htm. We acknowledge the contribution by Dr Richard Schoephoerster and the faculty of biomedical engineering at FIU.

[2] The numbers in parenthesis refer to bibliographical references with cited pages.

3.1 INTRODUCTION

The heart is among the most important organs in the human body. It is a complex muscular pump that maintains oxygen and blood circulation through the lungs and the rest of the body. The heart pumps about 7200 liters of blood in a single day and thus has a heavy workload. Its failure sometimes necessitates the implantation of artificial heart in the patient. The artificial organs have been used in clinical approaches to treat chronic illnesses for several decades. The use of the artificial kidney (dialyzer), artificial heart, cardiac pacemaker, artificial hips and knees, cochlear implants, and intraocular lenses offers treatment for a variety of cases. Numerous recent advances in the design and development of these systems have led to breakthroughs in the successful treatment of (what would otherwise be) fatal illnesses. It is, therefore necessary to:

1. **Understand and apply** basic terminology, theory, principles and knowledge of artificial heart, and its functions.
2. **Identify** the important issues, emerging technology, and clinical imperatives in the field of artificial heart.
3. **Evaluate** design criteria for artificial heart.
4. **Understand** the issues associated with the development and clinical trials for artificial heart and heart valves.
5. **Understand** the interaction between mechanical/electrical approaches to artificial heart designs and biological/cellular techniques.
6. **Understand** the issues associated with the development and selection of appropriate biomaterials used for artificial heart.
7. **Develop** an understanding of new therapeutic approaches to chronic illnesses.

Cardiovascular replacements encompass the following areas of study: Heart Assist Devices; Heart Replacement Systems; Vascular Replacement Systems; Tissue Engineered Systems (Bioheart); Cellular Repair and Replacement Systems; Heart Valve Replacement and Repair; and Cardiac Transplants.

3.2 DESCRIPTION OF THE HUMAN HEART

The heart has four chambers: right and left atria and right and left ventricles (Fig. 1). The two atria act as collecting reservoirs for blood returning to the heart while the two ventricles act as pumps to eject the blood to the body. The heart has four valves. See Appendix I for the description of the phases of "Cardiac cycle" and the description for ECG. See Appendix II for the example of Penn State TRH. Deoxygenated blood returns to the heart via the superior and inferior vena cava, enters the right atrium, passes into the right ventricle, and from here it is ejected to the pulmonary artery. Oxygenated blood returning from the lungs enters the left atrium via the pulmonary veins, passes into the left ventricle, and is then ejected to the aorta. The pumping action starts with the simultaneous contraction of the two atria. This contraction serves to give an added push to get the blood into the ventricles at the end of the slow-filling portion of the pumping cycle called "diastole." Shortly after that, the ventricles contract, marking the beginning of "systole." The aortic and pulmonary

valves open and blood is forcibly ejected from the arteries, while the mitral and tricuspid valves close to prevent backflow (Fig. 2). At the same time, the atria start to fill with blood again. After a while, the ventricles relax, the aortic and pulmonary valves close, and the mitral and tricuspid valves open and the ventricles start to fill with blood again, marking the end of systole and the beginning of diastole. Though equal volumes are ejected from the right and the left heart, yet the left ventricle generates a much higher pressure than does the right ventricle. The four heart valves are essential for the pumping action of heart. These allow blood to flow in one direction depending upon the pressure gradients and thus prevent a backflow of blood. Figure 2 shows the location of four heart valves.

Any damage to heart valves poses a significant health risk for that individual. The valves can be damaged due to a variety of reasons: Rheumatic heart disease, valve infection, and calcification/stiffness caused by long-term wear and tear. These can cause two major problems: 1. Stenosis: the valve does not open fully and this result in higher pressure gradients. 2. The insufficiency: the valve does not close properly and this causes a backflow of blood. In such cases, the heart becomes less efficient. Over time the increased load and strain may eventually cause the heart to fail and lead to death. The physician treating the disease has several options: Providing medications in order to improve the pumping action is a viable alternative. If the defect is serious then repairing the valve is an option. If the damage is such that it cannot be surgically repaired then only option is to replace the valve by an artificial valve for extending the life of a patient; however, there remains a consistent shortage of available donor hearts for transplantation. This has led research into the development of an artificial heart.

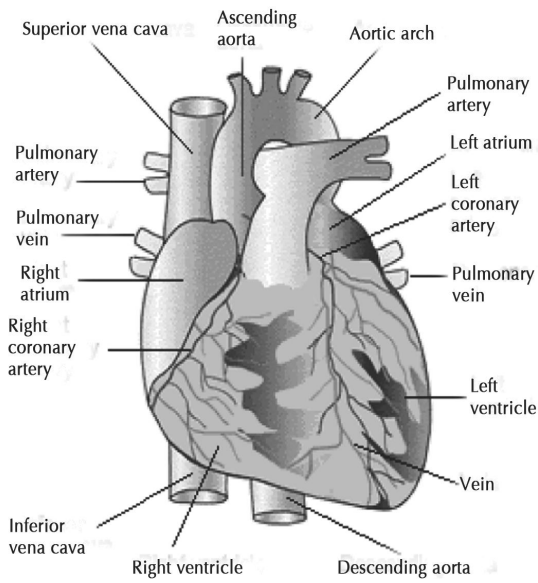

FIGURE 1 Internal structure of the human heart.

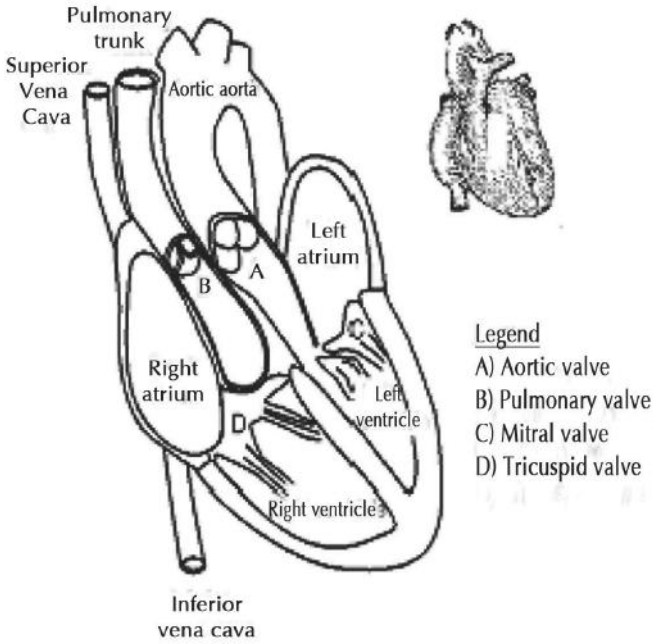

FIGURE 2 Anatomy of the human heart and 4 valves.

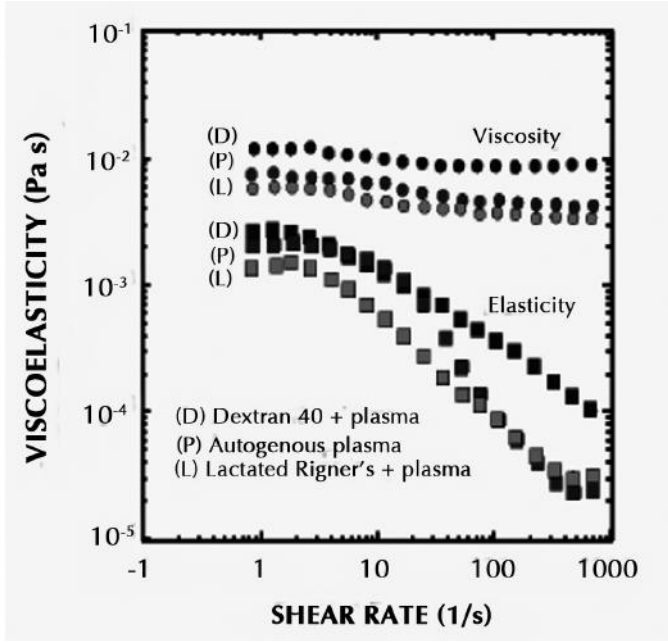

FIGURE 3 Changes in the rheology of blood as a result of cardiopulmonary bypass surgery.

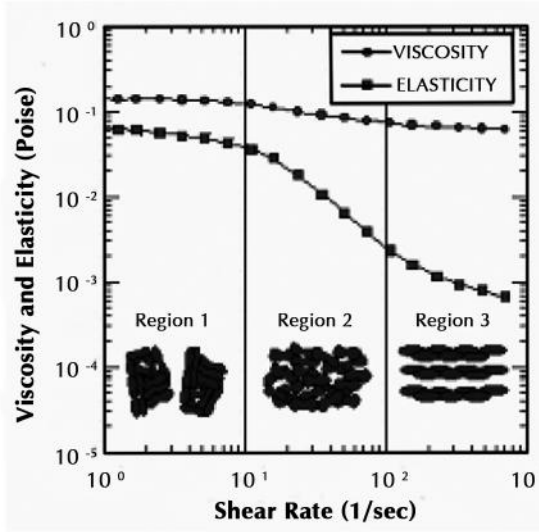

FIGURE 4 Rheology of the blood due to 50% dilution of the original plasma.

The Jarvik-7, named for its designer Dr. Robert Jarvik, functions like the natural heart. In 1982, surgeons at the University of Utah implanted Jarvik-7 in a patient named Dr.Barney Clark, who survived for 112 days. The longest survivor was William Schroeder, who was supported by the Jarvik-7 for 620 days. The Jarvik-7 was also called the Symbion total artificial heart (TAH). Today, it is called the Cardio West total TAH. Various models of artificial heart were subsequently developed such as Jarvik 2000, Akutsu TAH, Liotta TAH, and AbioCor TAH.

3.3 PROPERTIES, COMPOSITION AND FUNCTIONS OF BIOFLUIDS

Blood is a medium in which dissolved gases, nutrients, hormones and electrolytes are transported. It removes the waste products of metabolism like urea and ammonia ions. It provides protection against the toxins and pathogens (White Blood Corpuscles and antibodies). It also plays an important role in the stabilization of pH and temperature of our body. Finally, blood has the property of clotting that prevents the loss of blood from the body (14:15). Blood along with the heart and the blood vessels comprises the circulatory system of the body that helps in maintaining homeostasis. For example oxygen is picked up by blood as it passes through the lungs. This flows through successively narrower blood vessels: from arteries to arterioles and finally to the capillaries, where the oxygen rich blood delivers its oxygen to the cells. Figures 3 and 4 show how the rheology of blood is affected due to bypass surgery and due to dilution of plasma by 50%, respectively. Table 1 shows properties of human blood. All body fluids can be generally separated into two fluid compartments: the fluid found inside of cells (intracellular fluid) and the fluid found outside of cell (extracellular fluid) as shown in Fig. 5 and Table 2. Intracellular fluid makes up about 63% of all the fluid in our bodies while the remaining is the extra cellular fluid. Blood is composed of about

46–63% plasma that contains suspended cells. Plasma is the fluid component of the blood and is composed of 92% water, 7% proteins and 1% plasma solutes. Proteins include albumins; globulins, fibrinogen and hormones while the plasma solutes are composed of electrolytes, organic nutrients and organic wastes. The remaining 37–54% is the formed elements. Solid components in blood are specialized cells, such as:

1. **Red blood cells (RBC)** also called erythrocytes: RBC account for 99% of the formed elements. The male person has 4.5–6.3 RBC per cubic micro liter compared to 4.2–5.5 for a female.
2. **White blood cells (WBC)** also called leukocytes: The WBC provide defense against toxins and pathogens. This is a called nonspecific protection. They also provide specific defenses e.g. Defense against a specific antigen. There are 6,000–9,000 WBC per cubic micro liter in both males and females.
3. **The platelets** are basically cell fragments from an earlier cell. They initiate and control the clotting process. They clump physically to form a platelet plug causing a reduction in the site of injury and slow the blood loss. There are about 150,000 to 500,000 platelets per cubic micro liter.

TABLE 1 Typical values of properties of human blood (4).

Physical Property	Value (Average) and Range	Comments
pH	(7.31) 7.38–7.40	Arterial blood Venous blood
Relative viscosity	(3.00) 2.18–3.59	Inviter determination
Refractive index	(17.4) 16.2–18.5	—
Specific gravity	(1.058) 1.052–1.064	Copper Sulfate method used
Specific Heat, g-cal	(0.92)	—
Surface tension, dynes/cm	55.5–61.2	—
Colloid osmotic pressure, mm H_2O	(344) 310–376 (337) 300–373	Arterial blood Venous blood
Average Volume of blood in the body, mL	5000–6000	Varies with height, weight and age
Production rate mL/min	5000	

TABLE 2 Dissolved materials and their distribution (7).

Dissolved materials	Intra cellular fluid compartment	Extra cellular fluid compartment
Sodium	Low	**high**
Potassium	**High**	low
Calcium	Very low	**higher**
Magnesium	**High**	low
Chlorides	Low	**high**
Bicarbonates	Low	**high**
Phosphates	**High**	low
Sulfates	No real difference	—

TABLE 3 Values of extra cellular and intra cellular body water for a human (4).

Subject	Parameter	Value in mL/kg of body weight
Newborn	Extra cellular body water	353
2–9 months		267
Adult		158
Newborn	Intracellular body water	NA
2–9 months		NA
Adult		413

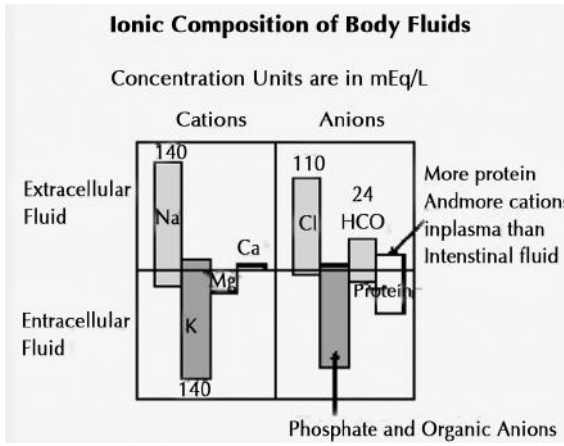

FIGURE 5 Ionic composition of body fluids.

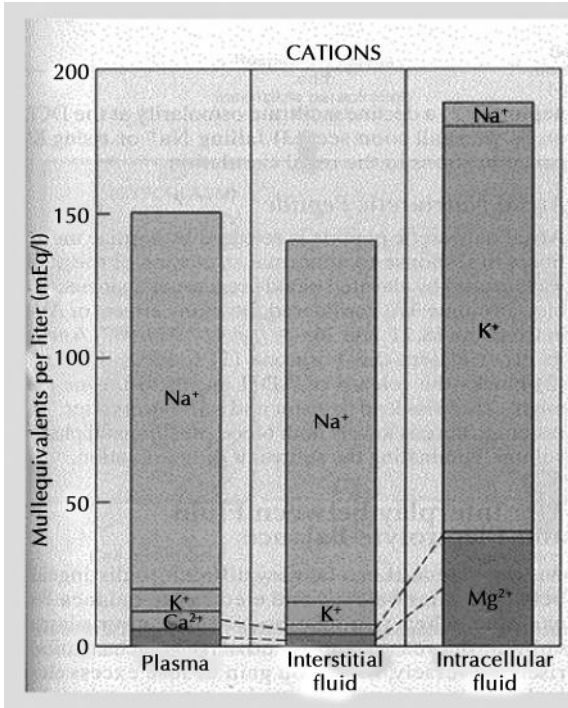

FIGURE 6 Composition of the body fluids for a 70 kg person (5).

Both fluids include the dissolved components, such as: Ions and organic materials like sugars, amino acids, and proteins. The functions of each of the dissolved materials are: Sodium and Potassium creates much of the osmotic pressure of extra cellular fluid and intracellular fluid, respectively. They are essential for electrical activity. Calcium is found in tissues and fluids and plays a role in blood clotting. Magnesium is essential for AdenineTriPhosphate production and activity of neurons and muscle cells. Chloride is the most abundant anion in extra cellular fluid regulates osmotic pressure. Sulfate is part of some amino acids and proteins in the form of sulfur. The electrolytes serve three functions. Firstly the electrolytes are needed for normal metabolism. Secondly, electrolytes are needed for proper fluid movement between semipermeable compartments (from cell to cell, from tissue to tissue, and from organ to organ). Fluids move through the process of osmosis from one compartment to another within fractions of a second. The concentrations and nature of the solutes in the fluids determines the fluid balance. Thirdly electrolytes help in maintaining the normal acid-base balance required for normal cellular activities. In normal human pH is between 7.35 and 7.45 and it is critical that this range is maintained. The amount of water and the concentration of electrolytes are important to bodily functions. When the body is "in fluid balance" it means that the various body compartments (cells, tissues, organs) contain the required amount of fluids to carry out normal bodily functions. The regulation of the body fluids is achieved through: Osmosis, Diffusion, and Filtration and

by the action of the Na-K pump. Figure 6 shows the composition of body fluids for a 70 kg person. Table 3 shows the values of extra cellular and intra cellular body water.

3.3.1 INTRAVENOUS FLUIDS

Intravenous (IV) fluids can supply fluid volume and electrolytes. These fluids are usually provided for expanding intravascular volume: To correct an underlying imbalance in fluids or electrolytes; to compensate for an ongoing problem that is affecting either fluid or electrolytes. Figure 7 shows components for transfer and delivery of IV fluids. Table 4 shows composition of IV fluids.

3.3.2 CRYSTALLOIDS

Conventional crystalloids are fluids that contain a combination of water and electrolytes. They are divided into "balanced" salt solutions (e.g.: Ringer's lactate) and hypotonic solutions. Either their electrolyte composition approximates that of plasma, or they have a total calculated osmolality that is similar to that of plasma. Common used colloids include albumin, hydroxyethyl starch (HES, also known as hetastarch: Hespan) and dextran. Colloid molecules are sufficiently large that they normally do not cross capillary membranes in significant numbers.

3.3.3 ARTIFICIAL BLOOD

3.3.3.1 BLOOD TRANSFUSION

A unit of blood is 450 milliliters (or 1 pint) and is mixed with chemicals (CPD) to prevent clotting. Each year, approximately 15 million to 20 million units of blood are donated in the United States. A health history is taken to ensure that the donor has not been exposed to diseases that can be transmitted by blood, and to determine if donating blood is safe for that person's own health. The donor's temperature, pulse, blood pressure and weight are obtained. A few drops of blood are obtained to make sure the donor is not anemic. It usually takes less than 10 min for the blood to be removed once the needle has been placed. Sterile and single-use equipment is used so there is no danger of infection to the donor (13). A loss of only 30% of blood volume in a patient, can lead to irreversible shock if not treated rapidly. There are many practical difficulties involved in blood transfusions. It requires many volunteers. A number of other factors have driven the need for a viable substitute for human blood, such as: The need to eliminate transfusion-related transmission of infectious disease; reduce the need for cross matching and related costs; and increase shelf life and stability at ambient temperatures. Artificial blood has many applications. It has uses, such as: In trauma, site of accidents, angioplasty and in heart surgery. Development of artificial blood products is a subject of ongoing research in many countries especially in Canada, Asia and Europe.

Patients requiring blood replacement need a short-term replenishment of the oxygen-carrying capacity of hemoglobin. This continues until the body can synthesize replacement of RBC. The hemoglobin requires refrigeration. Also it has a relatively short shelf life, and must be carefully matched for correct blood type and other factors. This trifold problem has intensified the efforts to develop hemoglobin alternative. It should have a capacity to be stored for a long period of time at room temperature and

transfused to restore the oxygen-carrying function of hemoglobin. There is a problem in delivering free hemoglobin. This is because hemoglobin, when separated from the red blood cells divides into halves, which lose the capacity to oxygenate the tissue. To overcome this problem, a cross-binding reagent is required. It should prevent the hemoglobin molecules from splitting after removal from the red blood cells. Attempts to develop blood substitutes have followed a number of different strategies. One involves extracting and chemically processing hemoglobin from donated human blood. This method does not require blood typing. However, it is still dependent on the availability of donated blood. The total market for artificial blood worldwide is estimated on the order of tens of billions of dollars.

Another approach is to develop genetically engineered hemoglobin molecule. It should be capable of releasing enough oxygen. Synthetic Blood International (SYBD: Kettering, Ohio, USA) has developed a blood substitute based on perflurocarbons. Blood gasses such as oxygen and carbon dioxide are highly soluble in perflurocarbons. SYBD's Oxycyte is intended to provide an effective means of transporting oxygen to tissues and carbon dioxide to the lungs. Compared with hemoglobin, Oxycyte has been found to be capable of carrying at least five times more oxygen. Additionally, perflurocarbons are considered to be more effective than hemoglobin for delivering oxygen at the tissue level. Also, the perflurocarbons micro droplets that carry the oxygen are 1/70th the size of the red cells. They can therefore reach many areas of the body that human RBC cannot. The product is inert and can be fully sterilized. It can be stored at room temperature and does not require typing and cross matching prior to use.

3.3.3.2 ANTICOAGULANTS

An anticoagulant is a drug that helps prevent the clotting (coagulation) of a blood. Anticoagulants are different from antiplatelet agents. Often, implantation of an artificial organ requires the use of anticoagulants such as Heparin or Coumarin. Patients fitted with artificial heart valves or who have atrial fibrillation are at a risk for forming blood clots. They are administered anticoagulants.

Antiplatelet agents are drugs that interfere with the ability of blood to clot. They are used to prevent blood clots from forming that can lead to heart attack or stroke. Antiplatelet agents work by preventing the platelets in the blood from clumping. Examples of antiplatelet include: aspirin, dipyridamole etc.

Heparin is an anticoagulant. It is a protein with a molecular weight ranging from 6,000 to 40,000 Da. Figure 9 indicates that Heparin has a unique five-residue sequence. It forms a high-affinity complex with antithrombin. This increases the rate of inhibition of two principle procoagulant proteases: factor Xa and thrombin. The normally slow rate of inhibition of both these enzymes ($\sim 10^3$–10^4 M^{-1} s^{-1}) by antithrombin alone is increased about 1,000-fold by heparin. The rapid inactivation of both the active forms of proteases prevents the subsequent conversion of fibrinogen to fibrin that is crucial for clot formation (Fig. 10). The action of Heparin is immediate and it is nontoxic. Heparin is generally given to postoperative patients and to those with acute infarctions requiring immediate anticoagulant action. In contrast, Coumarin is a principally oral anticoagulant. They exert their effects only after a latent period of 4 to 12 hr and the effects last for 1.5 to 5 days. Anticoagulant, citric acid, is used in vitro.

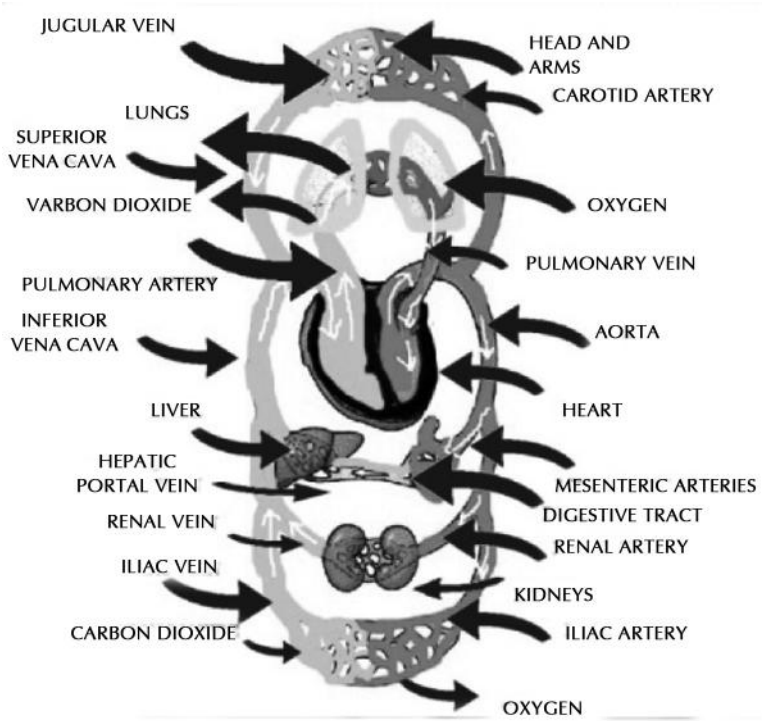

FIGURE 7 Components for transfer and delivery of intravenous fluids (11).

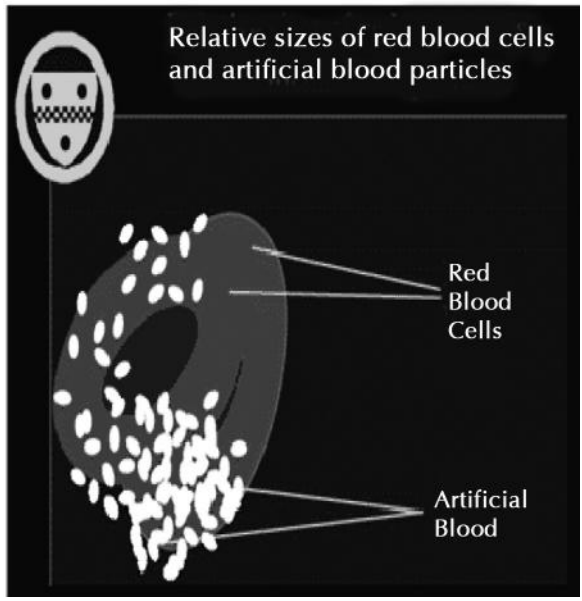

FIGURE 8 Comparison of the size of RBC and artificial blood particles (8).

TABLE 4 Composition of intravenous fluid (6).

Fluid	Na^+	K^+	Ca^{++}	Cl-	Other	pH
Crystalloids						
Bicarbonate 8.4%	1000	—	—	—	HCO3–1000	8
Dextrose 4%/saline 0.18%	30	—	—	30	Dextrose 40 g	4.0
Dextrose 5%	—	—	—	—	Dextrose 50 g	4.0
Hartmanns	131	5	2	111	Lactate 29 g	6.5
Saline (0.9%)	154	—	—	154	—	5.0
Colloids						
Albumin 4.5%	<160	<2	—	136	Albumin 40–50 g	7.4
Gelofusine	154	<0.4	<0.4	125	Gelatin 40 g	7.4
Haemaccel	145	5	6.25	145	Gelatin 35 g	7.4
Hetastarch (HES or Hespan)	154	—	—	154	Starch 60 g	5.5
Pentastarch	154	—	—	154	Starch 100 g	5.0

3.4 BIOMATERIALS

Biomaterials are required for the development of mechanical heart valves, pacemakers; vascular grafts, oxygenerators, and heart assist systems such as: total artificial hearts, intraaortic balloon pump, etc.

Mechanical heart valves are most commonly made from silicone elastomer, cobalt chrome based alloys, titanium and prolytic carbon. The prosthetic valves are made from materials of biological origin and are classified homografts or xenografts depending upon whether they are obtained from human species or nonhuman species (pig, cow), respectively. Stents are typically made from inert materials like nickel titanium, polyethylene tetraphthlate, polyurethane and various acrylate compositions. Pacemakers typically use a lithium-iodine battery, while the electrodes are made of platinum, stainless steel or cobalt alloys. The Intra Aortic Balloon Pumps use a polyurethane balloon; and helium or carbon dioxide are used to inflate it (16:283–296). Table 5 shows typical applications of common biomaterials. Future cardiovascular research in particular will focus on the development of cardiac materials that will eventually integrate with its biological environment. Such a device will release molecules similar to the organ it replaces, encourage entry and organization of the tissue cells within its structure and become completely or partially replaced by the host cells.

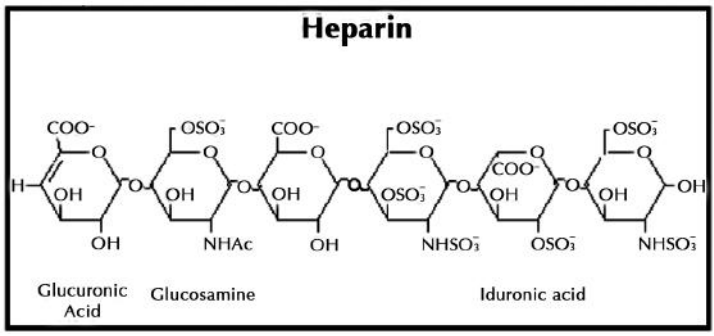

FIGURE 9 Residues of Heparin (9).

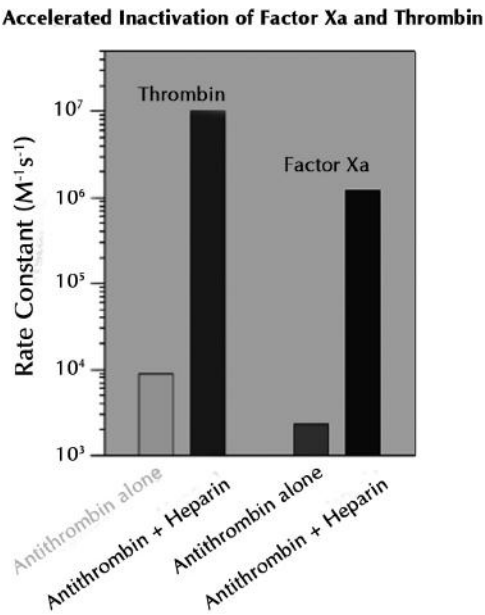

FIGURE 10 Effect of Heparin on the inactivation of Factor Xa and Thrombin (9).

TABLE 5 Typical applications of common biomaterials (17:14.3).

Biomaterial	Application
Bioactive coatings	Thrombo resistance.
Biodegradable macromolecules	Hemodialysis membranes, scaffolds for tissue engineering.
Biologically derived materials	Heart valves, vascular grafts.
Bioresorables	Sutures, catheter components.
Elastomer	Intra aortic balloon pump Artificial heart bladders.
Hydrogels	Catheter coatings.
Metals and alloys	Guide wires, biologic heart valve stents.
Plastics	Housings for extra corporeal devices.

3.5 MECHANICS OF BLOOD FLOW

The velicity of blood can be calculated using the continuity Eq. (1):

$$v = Q/A \tag{1}$$

Where: v = Mean velocity, Q = Volume flow rate and A = Cross-sectional area. For aorta, if Q = 100 mL/s and A = 3 cm^2, then v = 100/3 = 33.3 cm/s. Velocity is inversely proportional to the cross sectional area. Thus a reduction in the vessel diameter causes an increase in blood velocity. This might happen in "**aortic stenosis**." The velocity and pressure are related to each other. The dynamic pressure increases with increase in linear velocity. Total pressure is a sum of hydraulic pressure and dynamic pressure. This implies that the static pressure reduces with increasing velocity. From the physiological point of view, if the velocity goes really low due to "aortic stenosis" then the static pressure will reduce and can suck blood back from those arteries. This means that the blood flow to the heart is reduced thus resulting in a heart or chest pain. Hagen-Poiseuille's Law is defined in Eq. (2):

$$R \text{ a } (\Delta P/Q) = (8^* \text{ m } ^*L)/(\Delta r)^4 \tag{2}$$

Therefore: $Q\ a\ 1/L$; $Q\ a\ r^4$; and Q a 1/m.

Where: Q is the flow rate; L is the vessel length; r is the vessel radius; m is an absolute viscosity; and R is a hydraulic resistance. Poiseuille's Law is valid for steady, laminar and Newtonian fluid. Though the blood flow is not a steady flow yet it can be considered so, since the arterial system acts as a hydraulic filter to smooth out much of the pulsing. Thus the pulsing flow becomes a steady flow. Blood flow is usually laminar, however, it gets turbulent since pressure is proportional to the square of the flow. Blood is a nonNewtonian fluid; however, blood can be considered Newtonian fluid for shear rates greater than 50 per seconds. During ventricular contraction, work done by the heart is given by:

$$W = \Delta P * Q \tag{3}$$

Where: W = Work; ΔP = Pressure difference; and Q = Flow rate. Not all of the energy is used to cause the blood flow. Total energy follows "Law of Conservation Energy," and consists of potential energy (U), Kinetic energy (K), elastic energy, and as frictional losses (E).

$$W = K + U_{bl}OO_{d\ pressure} + U_aO_{rtal\ walls} + E_{dissipati}O_n \tag{4}$$

3.5.1 FLUID VELOCITY AND TURBULENCE IN BLOOD VESSELS

The pressure difference (ΔP) is the difference between the maximum and residual ventricular pressures. Assuming a maximum normal *systolic pressure of 120 mmHg* and a residual pressure of 9 mmHg, the pressure difference in the ventricle is 111 mmHg (or 1.5×10^5 dynes/cm^2). The stroke volume (V: the amount of blood expelled into the aorta during ventricular contraction) is about 80 cm^3. This means that the heart does about 1.18×10^{-7} ergs of work during a ventricular contraction. Only about 70% of this

work is done before the blood velocity reaches its maximum. So the amount of energy available to move blood at its maximum velocity is 0.83×10^{-7} ergs.

The pressure energy of the blood increases as the blood pressure increases from its diastolic to its systolic levels. Assuming a **normal diastolic pressure of 80 mmHg**, the pressure difference in the blood is 40 mmHg, or 5.3×10^{-4} dynes/cm ^{2}. At 70% of the stroke volume will have 2.99×10^6 ergs of energy in the increased blood pressure. In addition, potential energy is stored in the arterial walls as they expand. Assuming the Hookean behavior with a spring constant of $k = 1.25 \times 10^{-6}$ dynes/cm and a variation in radius of 0.2 cm in the aorta, we will have 2.5×10^{-4} ergs of elastic energy.

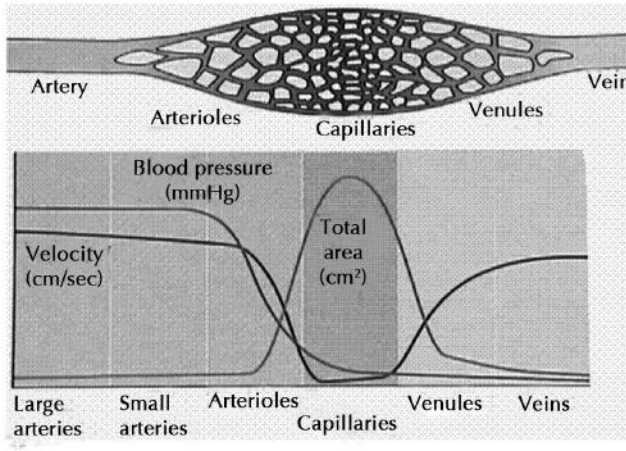

FIGURE 11 Velocity of blood in arteries, capillaries, venules and veins (20).

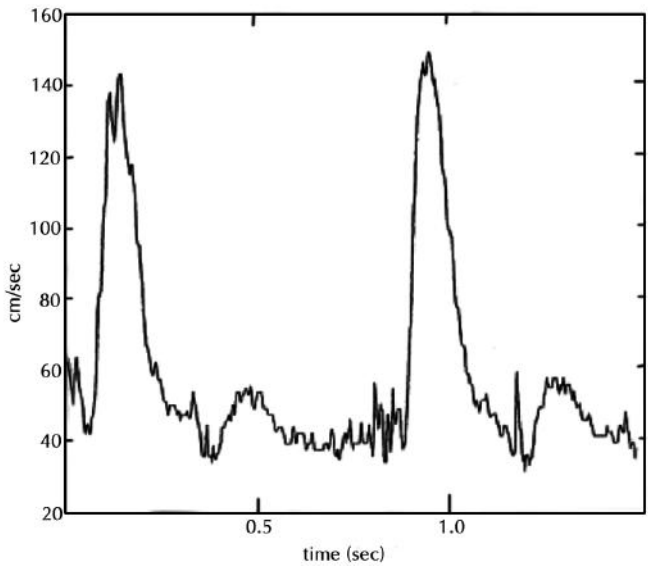

FIGURE 12 Graphical representation of blood flow through a blood vessel (19).

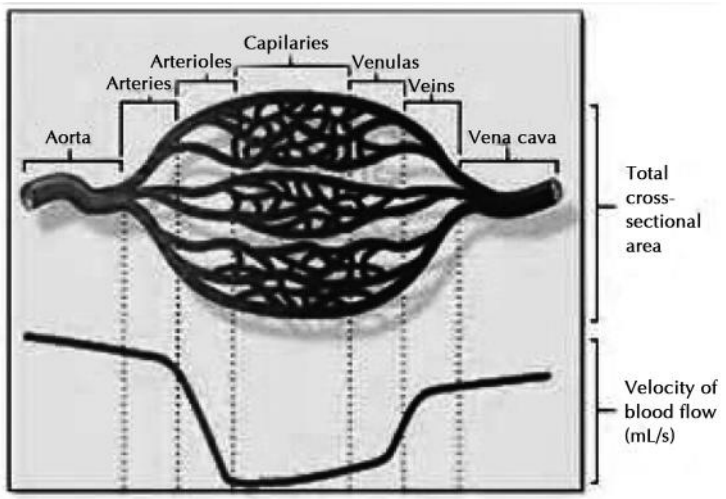

FIGURE 13 Velocity of blood versus radius of the vessel (20).

Poiseuille's equation is used to calculate the pressure loss along the aorta and then the energy loss due to dissipation is computed using the stroke volume. Assume a flow rate of 96 cm^3/s. The average radius of the aorta is 1.25 cm, and its length is approximately 30 cm. Therefore, the pressure drop along the aorta will be 120.2 dynes/cm^2. It implies that energy lost in dissipation is 9.6×10^{-3} ergs. This being a negligible amount, dissipation loss in the aorta can be ignored for the purpose of computing aortal velocity. Hence velocity can be computed as follows:

$$K = W - U_{bl} OO_{d\ pressure} OR \tag{5}$$

$$(1/2)\ ((\rho)(0.7\ V))\ v^2 = 8.29 \times 10^{-6} - 2.99 \times 10^{-6}\ \text{ergs}$$

Where: ((ρ)*(0.7 V)) is a mass of the blood moved during one heartbeat. Solving Eq. (5), we have a blood velocity, v = 425 cm/s. In a normal patient, the velocity rises sharply and drops again to zero within the first quarter of the heartbeat, during pulsatile flow. Fluid flow in a vessel crosses the threshold from laminar to turbulent flow when «Reynolds's Number» (Re) reaches about 2,000. Re is a ratio of the inertial force to viscous force (Eq. (6)):

$$\text{Re} = ((\rho)^*(L)^*\ (v))/(\text{m}) \tag{6}$$

Where: v = Velocity of the fluid; L = the characteristic "length" of vessel; ρ = Fluid density; and μm = Fluid absolute viscosity. The inertial forces tend to keep the fluid flowing, while the viscous forces tend to slow the motion due to friction with adjacent layers of fluid. Its value indicates the relative unimportance of viscosity, for example, low Re corresponds to very viscous situations. For a value of 425 cm/sec for aortal velocity computed above, Re is 28,000 in the aorta. This value is rather misleading. While Re reaches this value, it might indicate the presence of turbulence in the aorta.

It is not clear how long Re remains that large. If it is not that high for an adequate time to form macroscopic eddies, one would not expect to detect the turbulence. The eddy advection time is:

$$t_a = ((V * \Delta t)/K)^{0.5} \quad (7)$$

Where: Δt = Time duration of a heartbeat; K = Kinetic energy of the blood; and V = Stroke volume. Using the above computations, we find $t_a = 0.7$ milliseconds. The eddy length scale (which tells us the size of an eddy) that can form is 0.7 milliseconds. The eddy length scale (l_a) for the above results is about 5.2×10^{-3} cm. This indicates that small eddies are being formed and dissipated in very short lengths of time.

In normal patients, the velocity reaches its peak and falls in approximately 0.2 sec. It seems from the dependence of t_a and L_a that the length scales as the square root of the time. Therefore, the expected aortal eddy size is 0.09 cm. The magnitude of this value indicates that normal flow in the aorta is laminar, but on the verge of turbulence.

Certain assumptions are made during the computations of the energy output of the heart: The equation is only valid if the ventricular contraction is instantaneous, since the volume is assumed to be constant. A constant volume of blood undergoes a change in pressure, and then is placed instantly into the aorta. Heuristic approach to compensating for this simplification was to say that only 70% of the work done by the heart is done by the time, the blood reaches its maximum velocity. The walls of the aorta are elastic and follow Hook's Law. While the aortal walls have very high resilience, the stress versus strain curve is not linear throughout the range of radii during pulsatile flow. Since the normal radial variation is on the order of plus or minus eight percent, it can be justified that our assumption does not deviate too far from Hookean behavior. Finally, in using Poiseuille's law and Reynolds's number for pulsatile flow in flexible blood vessels, equations designed for constant flow through straight and rigid tubes are assumed. In the case of Poiseuille's law the results, even though are only reasonable to order of magnitude, and are of negligible order. Similarly, Reynolds's number is only useful in situations where the velocity is essentially constant over time. This is why one has to examine the eddy time and length scales.

3.6 COMPUTATIONAL FLUID DYNAMICS (CFD)

CFD is a computational technology to study the dynamics of flow. CFD enables sophisticated analysis to predict fluid flow behavior as well as heat transfer, mass transfer (e.g., perspiration, dissolution), phase change (e.g., freezing, boiling), chemical reaction (e.g., combustion), mechanical movement (e.g., impeller turning), and stress or deformation of a related structure. CFD allows the user to build a computational model that represents a system or device (e.g., Artificial Heart). Then fluid flow physics is applied to the device, and the software outputs a prediction of the fluid dynamics (20:21). CFD is a versatile tool for the prediction of detailed flow patterns: Regions of stagnant; Re-circulating fluid; detailed pressure variations; and shear stresses in the fluid and at boundaries. The use of CFD analysis streamlines the design and manufacture of the "Total Artificial Heart (TAH)." CFD provides detailed performance assessment, thus saves time and money for experimentation. CFD is a valuable tool for device design and manufacturing processes by simulating various physiological flows,

including ones that interact with the actual medical devices. Flow modeling provides engineers with the ability to accurately determine the performance of design concepts, reducing the need for physical testing and building of prototypes. This allows the engineering team to evaluate more designs with less cost and more efficiency. Finally, it results in a substantial improvement in performance. At the same time, the lower cost and shorter lead-times of development work provide speed to market and reduced development costs (20, 21). The flexibility of CFD analysis also provides an efficient method of carrying out sensitivity studies on key design parameters. Such analyzes can identify which parameters are the most significant for device design. We engineers use CFD for following reasons:

1. **Insight:** There are many devices and systems that are very difficult to prototype. Often, CFD analysis shows the parts of the system or phenomena happening within the system that would not otherwise be visible through any other means.
2. **Foresight:** CFD is a tool that predicts what will happen under a given set of circumstances. It can answer many 'what if?' questions. All of this is done before physical prototyping and testing. The foresight one gains from CFD helps to design better and faster.
3. **Efficiency:** Better design leads to shorter design cycles. Time and money are saved. CFD is a tool for compressing the design and development cycle.

3.6.1 COMPUTATIONAL FLUID DYNAMICS FOR ARTIFICIAL HEART

Cardiovascular simulation is a coupled problem. Not only the blood is a nonhomogeneous, anisotropic, nonNewtonian fluid, but also the boundaries of the flow, (the arteries, veins, heart, etc.) are not rigid, and in many instances can have a pronounced effect on the flow. Therefore predictions are not possible using rigid wall, or prescribed-boundary-motion approximations.

On a more fundamental level, the modeling of fluid transport in organ systems leads to a better understanding of physical mechanisms that contribute to the development of certain diseases or medical conditions. For example, researchers at the Thomas Jefferson University modeled blood flow in arteries to predict the growth and rupture risk of cerebral aneurysms. Aneurysm is caused by weakness of the arterial wall resulting in a balloon-shaped bulge in the artery. The arterial wall weakness may be caused by abnormally large flow shear stresses that damage wall cells. Once an aneurysm is formed, the blood flow within it may induce vibrations of the aneurysm wall that will progress and eventually rupture (22). The simulation of blood flow with CFD provides more information than current diagnostic tools for the flow patterns for a prototype (See Figs. 14 and 15). As CFD analysis is further developed into a practical diagnostic tool, it is expected to dramatically improve the ability of physicians to weigh the results of alternative treatment methods. The exacting demands posed by the human body on the artificial organs require a quantum paradigm shift from conventional methods. This uses the latest computer tools from aerospace (e.g., CFD, CAD) for "Rapid Prototyping the design of medical devices." Some of the active areas of research include: constitutive modeling of blood, computer simulation of transport, advanced flow visualization, blood damage modeling, computerized optimization of

shape, methods of control and power generation, and a multidisciplinary design (See Figs. 16 to 18).

3.7 DEVELOPMENT OF THE ARTIFICIAL HEART

The milestones in the development of artificial heart are shown below:

Year	Scientist/agency	Remarks
1953	John Gibbon	A heart-lung machine designed by physician John Gibbon is used in open-heart surgery
1964	——	The National Heart, Lung and Blood Institute sets a goal of designing a total artificial heart by 1970
1964	Hardy	Unable to sustain the cardiac cycle and support circulation
1966	Dr. Michael DeBakey	He successfully implants a partial artificial heart at Houston.
1967	Dr. Christiaan Barnard	Internal bleeding 24 hr post surgery. He transplanted the first human heart transplant.
1967	Dr.Adrian Kantrowitz	Death was due to rejection of the heart
1968	Dr. Barnard	Successful
1969	Dr. Denton Cooley	A total artificial heart is implanted into a patient at the Texas Heart Institute. The patient gets a heart transplant three days later but dies more than a day later.
1980	Dr. Shumway, Dr.Lower	Incidence of rejection and infection decreased
1982–85	Dr. William DeVries	He carried out a series of five implants of the Jarvik total artificial heart. The first patient, Barney Clark, survives for 112 days. Only four others received the Jarvik as a permanent replacement heart: William Schroeder, lived 620 days. Other patients receive the Jarvik as a temporary device while awaiting transplants.
1984	Dr. DeVries, Dr. Semb	Successful
1994	FDA	The Food and Drug Administration approves the Left Ventricular Assist Device, which helps failing hearts continue to function.
2000	—	A man in Israel becomes the first recipient of the Jarvik 2000, the first total artificial heart that can maintain blood flow in addition to generating a pulse.
2001	—	Doctors at Jewish Hospital in Louisville implanted the first self-contained, mechanical heart replacement. The device, called the AbioCor, was battery powered and was the size of a softball.

3.7.1 PIONEERING PATIENTS WHO HAD A HEART TRANSPLANT

A heart transplant or a cardiac transplantation is a surgical transplant procedure performed on patients with end-stage heart failure or severe coronary artery disease. **Norman Shumway** is widely regarded as the father of heart transplantation although the world's first adult human heart transplant was performed by Christiaan Barnard in South Africa using the techniques developed and perfected by Norman Shumway and Richard Lower. Median survival time is 10 years for heart transplant. Some well-known patients are listed below (List is not complete):

1967, December 3: Christiaan Barnard performed the world's first adult heart transplant on Louis Washkansky at the Groote Schuur Hospital in Cape Town South Africa.

1967, December 10: Adrian Kantrowitz performed the first pediatric heart transplant in the world at Maimonides Hospital (now Maimonides Medical Center) in Brooklyn, New York.

1968, January 6: Norman Shumway performed the first adult transplant in the United States on January 6, 1968 at the Stanford University Hospital.

1969, April 4: Haskell Karp of Skokie-IL received an artificial heart at St. Luke's Episcopal Hospital in Houston. Dr. Denton Cooley did the procedure. The patient lived 65 days with the externally powered heart while awaiting a donor heart, but died 30 hr after receiving the transplant.

1978: Tony Huesman Huesman received a heart in 1978 at the age of 20 after viral pneumonia severely weakened his heart. The operation was performed at Stanford University under heart transplant pioneer Dr. Norman Shumway. At the time of his death due to cancer on August 10, 2009, Tony Huesman was the world's longest living heart transplant recipient, having survived for 31 years.

1981, **July 23:** Willebrordus Meuffels received an externally powered artificial heart at St. Luke's Episcopal Hospital. The heart kept the Dutch Tour bus driver alive for 54 hr until he received a heart transplant on July 26. But Meuffels died on August 2 with massive infection and organ failure. FDA told Cooley that further use of artificial hearts would require advance approval.

1982, December 2: Barney Clark was dying of heart failure when he received a Jarvik-7 artificial heart in Salt Lake City. He returned to surgery twice because of complications and suffered seizures and pneumonia before dying of multiorgan failure on March 23, 1983. "It was a struggle throughout the 112 days. He looked at it as one in a long series of experiments. He knew eventually he would die on the device," said Don Olsen, one of the Utah researchers who led the study.

1984, April 8: Fiona Coote was the second Australian to receive a heart transplant in at age 14 and the youngest Australian. In the 24 years after her transplant she became involved in publicity and charity work for the Red Cross.

1985, February 17: Murray Haydon, a retired auto worker, became the third recipient of the Jarvik-7. He died at age 59 after 488 days on the heart. He left the hospital

briefly on three occasions, but spent most of his time in the Humana intensive care unit. Haydon died of kidney failure on June 19, 1986.

1985, April 7: Leif Stenberg of Sweden, received an artificial heart in his native country, and survived 229 days until November 21. He was able to leave the hospital and even eat in restaurants. But he died of a massive stroke.

1985, April 14: Jack Burcham received an artificial heart at Humana. He died 10 days later of bleeding complications.

1985, November 25: William Schroeder was the second Jarvik-7 recipient and lived the longest, 620 days, after the pump was implanted, at the Humana Heart Institute in Louisville, KY. He died after a series of strokes impaired his ability to breathe. He was the first patient to live outside the hospital with the artificial heart.

1988, September 23: Kenneth Claus had a heart transplant at Shands Hospital, Gainesville, Florida and was ranked by 19th as one of the top 25 professors for the U.S. in 2009–2010. He still teaches 3 semesters a year at Florida International University, Miami, FL, USA.

1990: Carroll Shelby **(**American entrepreneur famous for his race car driving and automotive developments in designing the cult-classic Shelby Cobras and Ford's Shelby Mustang) received a heart transplant in 1990, then in 1996, a living donor kidney transplant from his son. He died May 10, 2012 at the age of 89.

1991, **September 3:** Mike Templeton received an experimental HeartMate (Left ventricular assist device) at St. Luke's Episcopal Hospital. He lived for 16 months. Eventually, he was able to visit his family at home and spend some time out of the hospital. He was awaiting a transplant when he died of a stroke on January 19, 1993.

2008, September 20: Glen Gondrezick (American basketball player, formerly in the NBA, and broadcaster) received heart transplant and died on April 27, 2009.

2009, November 20: Roberto Julio Sánchez (Singer and actor known as "Sandro of America") had a heart – lung transplant and died on January 4, 2010.

2012, March 20: Dick Chiney, Vice President under George W. Bush, received his heart transplant on March 24, 2012 at Inova Fairfax Hospital.

3.7.2 ABIO COR™ IMPLANTABLE REPLACEMENT HEART

The AbioCor is the first completely self-contained total artificial heart developed by ABIOMED Inc. and its collaborators, with the support of the National Heart, Lung and Blood Institute (Figs. 19 and 20). It consists of a hydraulic pump for transporting hydraulic fluid from side to side and a hydraulic pump rotating at approximately 10,000 rpm. Valve opens and closes to let the hydraulic fluid flow from one side of the artificial heart to the other side. When the fluid moves to the right, blood gets pumped to the lungs through an artificial ventricle. When the fluid moves to the left, blood gets pumped to the rest of the body.

A rechargeable battery is implanted inside the patient's abdomen. This gives a patient 30 to 40 min to perform certain activities, such as showering, while disconnected from the main battery pack. The internal components include an electronic controller implanted in the patient's abdominal wall. It monitors and controls the pumping speed of the heart. The external component is the battery pack that can operate for 4 hr. Power to the AbioCor is achieved with a Transcutaneous Energy Transmission (TET) system. The TET system consists of internal and external coils that are used to transmit power via magnetic forces from an external battery across the skin. The internal coil receives the power and sends it to the internal battery and controller device. Because tubes or wires do not pierce the skin, the chances of developing an infection are minimal. The patient using AbioCor must meet the following criteria:

- Have end-stage heart failure.
- Have a life expectancy of less than 30 days.
- Not eligible for a natural heart transplant.
- Have no other viable treatment options

3.7.3 JARVIK-7 TOTAL ARTIFICIAL HEART (TAH)

The Jarvik-7 was designed by Dr. Robert Jarvik to function like the natural heart (Fig. 21). Today, it is called the CardioWest TAH and is used in selected centers as a bridge to transplantation. The Jarvik-7 has two pumps, much like the heart's ventricles. Each sphereshaped polyurethane "ventricle" has a disk-shaped mechanism that pushes the blood from the inlet valve to the outlet valve. Air is pulsed through the ventricular air chambers at rates of 40 to 120 beats per minute. The artificial heart is attached to the natural atria by cuffs made of Dacron felt. The drivelines out of the ventricular air chambers are made of reinforced polyurethane tubing. The lines are covered where they exit the skin with velour-covered Silastic to ensure stability and encourage tissue growth.

The air-driven, external power system powers the pump through drivelines that enter the heart through the left side of the patient. The large console on wheels is as large and as heavy (but not quite as tall) as a standard household refrigerator, and is normally connected to sources of compressed air, vacuum, and electricity. The system is backed up by a rechargeable battery in case of a power failure and includes on-board compressed air tanks (modified scuba type) for use during patient transport. Controls in the console allow the doctor to control pump rate, pumping pressure and other essential functions.

FIGURE 14 CFD flow analysis for Artificial Heart: De Bakey VAD (23).

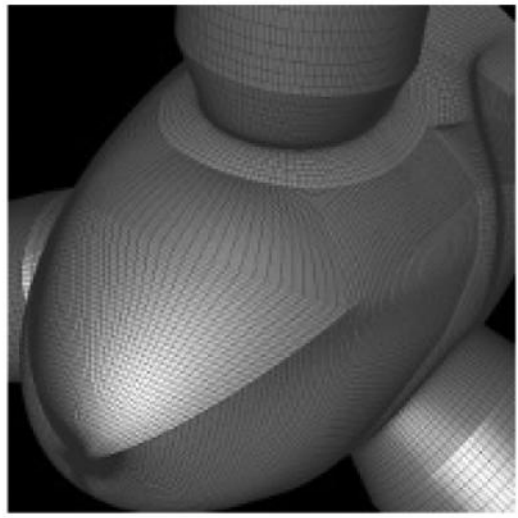

FIGURE 15 CFD low analysis in Artificial Heart: DeBakey VAD (23).

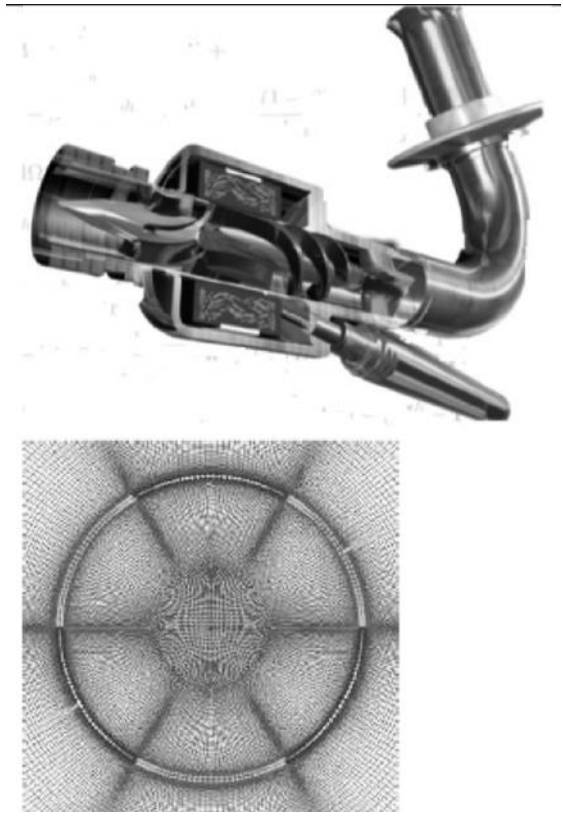

FIGURE 16 CFD flow analysis of bearing design for DeBakey VAD (23).

FIGURE 17 CFD flow analysis of bearing design for DeBakey VAD (23).

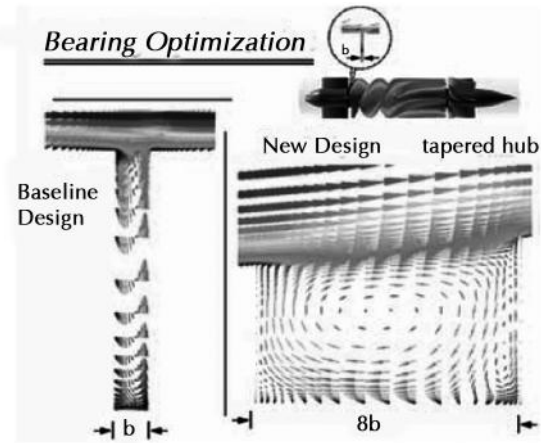

FIGURE 18 CFD flow analysis optimization of design for DeBakey VAD (23).

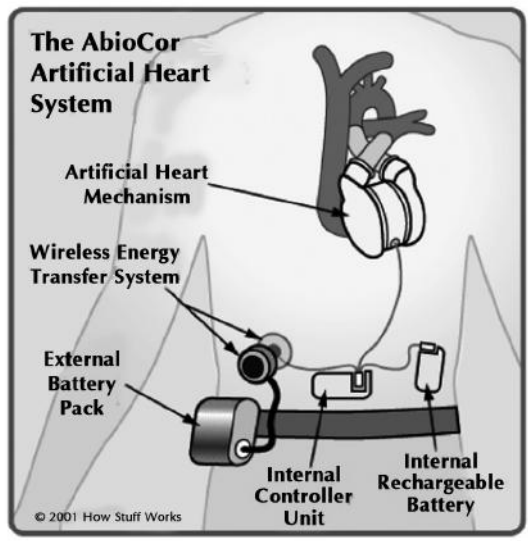

FIGURE 19 The AbioCor artificial heart system (29).

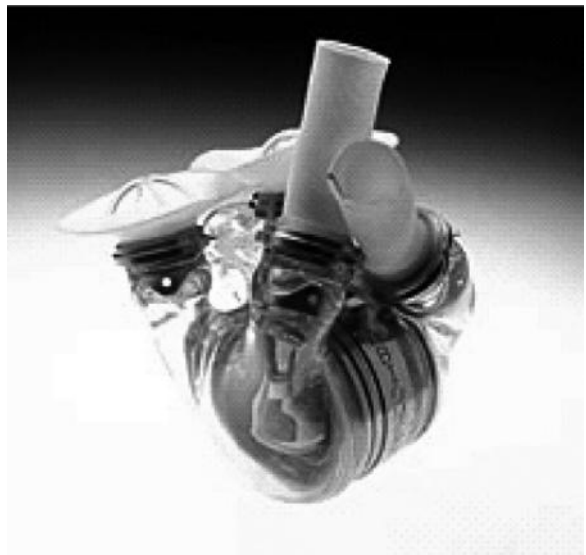

FIGURE 20 AbioCor implantable replacement heart (29).

Jarvik 2000 (Fig. 22)

Jarvik Heart Inc. and the Texas Heart Institute began developing the Jarvik 2000 in 1988. About the size of a "C" battery, the device is a valveless, electrically powered axial flow pump that fits directly into the left ventricle and continuously pushes oxygen-rich blood throughout the body. The Jarvik 2000 is an axial flow blood pump that uses electrical power to rotate a vaned impeller—its only moving part. The device is 2.5 cm wide × 5.5 cm long, and weighs 85 grams. The impeller is a neodymium-iron-boron magnet, which is housed inside a welded titanium shell. The impeller is supported by ceramic bearings. A small cable, which exits the body through the abdominal wall, delivers power to the impeller. All of the blood-contacting surfaces are made of highly polished titanium. The normal operating speed ranges from 8,000 to 12,000 rpm that will generate an average pump flow rate of 5 liters per minute. An analog controller controls the pump speed. The pump speed can be manually adjusted from 8000 to 12000 rpm in increments of 1000. The control unit monitors the pump function and the remaining power in the batteries. Audible and visual alerts notify the user of any problems.

FIGURE 21 Jarvik-7 Total Artificial Heart (30).

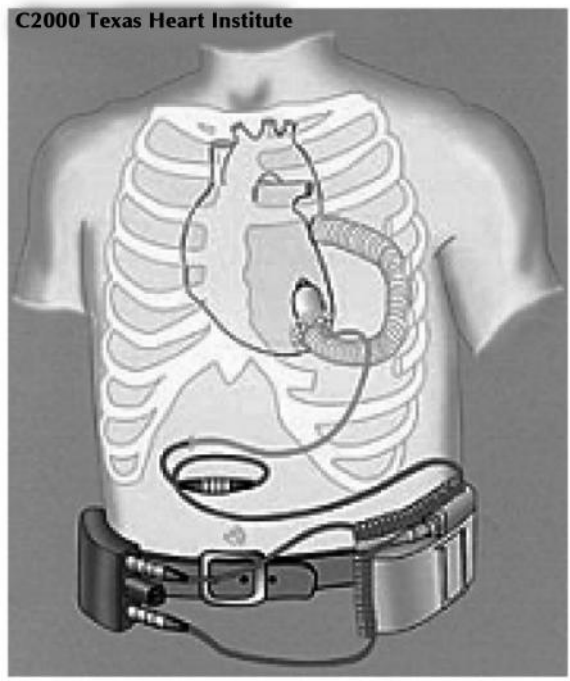

FIGURE 22 Jarvik 2000 (31).

3.8 ABIOMED BVS-5000®

The ABIOMED BVS-5000 is used worldwide for temporary left, right, or biventricular (both ventricles) support in patients with potentially reversible heart failure. The BVS-5000 underwent preclinical studies at the Texas Heart Institute (THI) from 1986 to 1988 and was introduced for use in patients at THI in 1988. It was the first heart assist device approved by the U.S. Food and Drug Administration for the support of postcardiotomy patients (those who have developed heart failure as a result of heart surgery). Since that time, hundreds of patients have been sustained by the BVS-5000, with durations of support up to 63 days. In addition to postcardiotomy support, the BVS-5000 may also be used in the following cases:

1. Donor heart dysfunction or donor heart failure after heart transplantation.
2. Right-sided heart failure after placement of a left ventricular assist device.
3. Acute heart attack.
4. Acute heart disorders, such as viral myocarditis.
5. Trauma to the heart.
6. Disease of the heart muscle (cardiomyopathy).

In patients whose hearts have not recovered after temporary support, the BVS-5000 may be used as a bridge to another device or as a bridge to heart transplantation. This air-driven blood pump is placed outside the body (extra corporeally). A unique feature of this system is its dual-chamber design, which is similar to the natural heart. This design provides support for either the left or right ventricle, or both. The pump houses two polyurethane chambers: an atrial chamber that fills with blood through gravitational force and a ventricular chamber that pumps blood by air-driven power. The atrial chamber is vented outside the patient. The ventricular chamber is connected to the power console by a 0.25-inch pneumatic (air) line. Two trileaflet valves separate the atrial and ventricular chambers. The pump can produce blood flow up to 5 liters per minute. The BVS-5000 console can support one or two blood pumps. It is fully automatic and compensates for changes both in preload and after load. The left and right sides are triggered independently of each other. A backup battery provides 1 hr of support, and an alarm will sound when only 10 min of power remain. A foot pump can also serve as a backup power source. By using the console to limit blood flow, patients can be slowly weaned from support.

3.8.1 INTRA-AORTIC BALLOON PUMP (IABP)

Dr. Adrian Kantrowitz introduced the intraaortic balloon pump (IABP) in the late 1960s to increase coronary perfusion. Because it was easy to insert, the IABP was the most widely used form of mechanical circulatory support. At the THI, the IABP is now used in more than 450 patients each year. Although the IABP was first used for surgical patients, the pump can now be used along with interventional cardiology procedures and medical therapy (medications). Indications for its use include:

1. Failure to wean from cardiopulmonary bypass.
2. Cardiogenic shock.
3. Heart failure.
4. Acute heart attack.

5. Support during high-risk percutaneous transluminal coronary (balloon) angioplasty, rotoblator procedures, and coronary stent placement.

The IABP is a polyethylene balloon mounted on a catheter, which is generally inserted into the aorta through the femoral artery in the leg. The pump is available in a wide range of sizes (2.5 mL to 50 mL). The balloon is guided into the descending aorta, approximately 2 cm from the left subclavian artery. At the start of diastole, the balloon inflates, augmenting coronary perfusion. At the beginning of systole, the balloon deflates. The blood is ejected from the left ventricle, increasing the cardiac output by as much as 40 percent and decreasing the left ventricular stroke work and myocardial oxygen requirements. In this manner, the balloon supports the heart indirectly. The balloon is inflated with helium, an inert gas that is easily absorbed into the bloodstream in case of rupture. Inflation of the balloon can be triggered according to the patient's electrocardiogram, the blood pressure, a pacemaker (if they have one), or by a preset internal rate. The balloon pump console drives the IABP. The operating controls are located on a touch pad below the display monitor and can be programed to produce rates as high as 140 beats per minute. The on-board battery provides power for up to 2 hr.

3.8.1.1 CARDIAC ASSIST DEVICES

The human heart is a pump that consists of 4 chambers. The ventricles are power pumps and act as the major pumping chambers. The coordinated and efficient pumping of the heart is possible due to the natural pacemaker. The Sino Atrial Node also called the natural pacemaker controls the rate of heartbeat and the pumping action of the heart. The electrical signal originates at the SA node. From there, the pulse travels to the atrioventricualr node (AV node) through the atria. The AV node is located at the junction of the atria and the ventricles. It serves as a delay line, which ensures that the atrial contraction is complete before the ventricular filling starts. From the AV node the impulse propagates to the "Bundle of His," which is composed of the left and right bundle branches. These are conducting pathways that spread out into the ventricles. Finally the impulse spreads to the Purkinje fibers, which conduct the impulse throughout the ventricles. However, sometimes the natural pacemaker property of the SA node may be lost due to damage to the SA node or atria. On other occasions the presence of heart blocks may prevent the signal from traveling its full path. In such a case, it is essential to provide artificial stimulation to the heart muscles. This is done with the help of a pacemaker.

A pacemaker is a small electronic device that regulates the heart beat by sending electrical signals to the heart. Figure 25 shows the heart and the pacemaker. It has two parts: A battery-powered generator and the wires that connect it to the heart. The generator is about the size of a silver dollar and has an effective life of seven to 12 years. It is implanted just beneath the skin below the collarbone. The leads are threaded into position through veins leading back to the heart. These leads carry electrical signals from the pacemaker to the heart. The most commonly used pacing device is the demand pacemaker. As the name suggests it provides pulses only when there is a demand for them. It monitors the pacing activity of the heart and provides pulses only of the beats per minute fall below a minimum value, which can be decided beforehand. It is

usually set to 60 BPM. People with pacemakers can do most normal activities: Drive a car, bathe, swim, or play noncontact sports. Pacemakers are protected from electrical interference and there are no problems with microwave ovens, televisions and most electrical tools. Medicines also do not interfere with the functioning of the pacemaker.

A Cardioverter is also called an Implantable Cardioverter Defibrillator (ICD). It is similar to a pacemaker with some additional functions. The ICD monitors the heart rhythm and delivers the programed treatment. In case of ventricular tachycardia that is not too fast, the ICD can deliver several pacing signals in a row. When those signals stop, the heart may go back to a normal rhythm. This is called pacing. If the pacing does not work, cardioversion can be used wherein a mild shock is sent to the heart to stop the fast heartbeat. If ventricular fibrillation is detected, a stronger shock is sent. This stronger shock can stop the fast rhythm and help the heartbeat go back to normal. This is called fibrillation. Finally the ICD can also check when the heart beats too slowly. It can act like a pacemaker and bring the heart rate up to normal.

Ventricular Fibrillation is the condition when the heart stops pumping blood to the brain and the body. Ventricular Fibrillation occurs without warning and can have fatal consequences. This condition is treated with an external defibrillator. A defibrillator consists of 2 paddles that are pressed on the outside of the chest and they deliver a shock to the patients' heart. This shock stops the irregular heartbeat and helps the heart recover its rhythimicity.

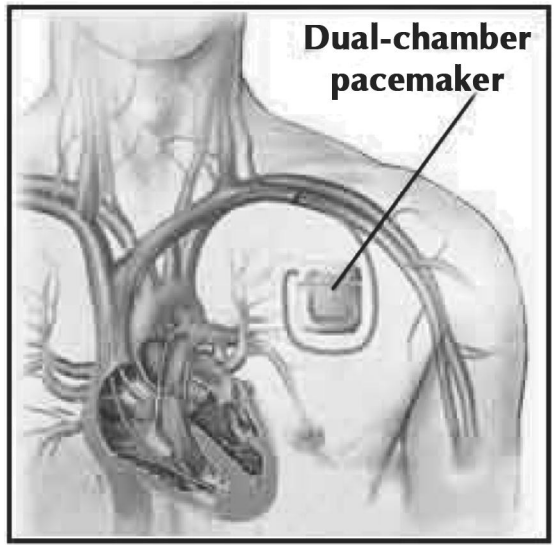

FIGURE 23 Pacemaker and the heart (24).

FIGURE 24 Bioheart's Myoblasts technique (25).

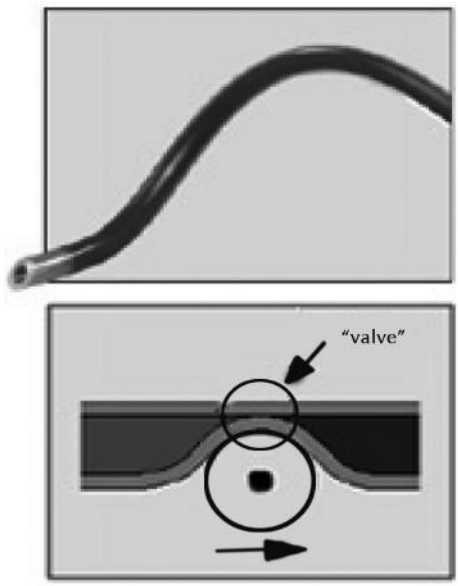

FIGURE 25 Peristaltic pump and the roller (26).

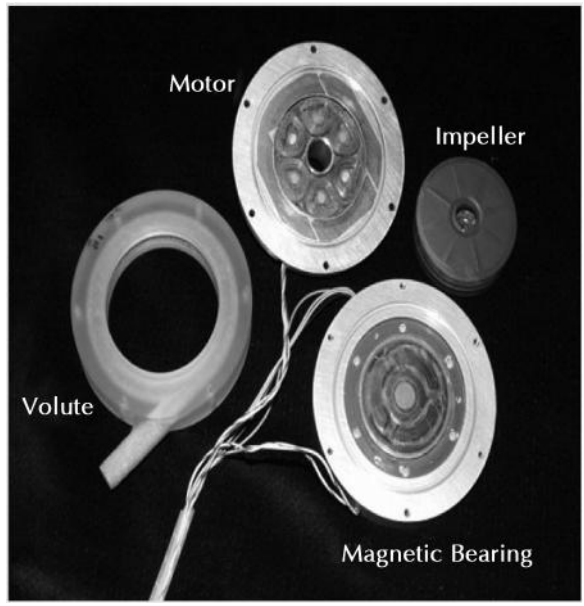

FIGURE 26 Inherently controllable blood pump developed by Foster Miller Technologies (27).

3.8.2 LEFT VENTRICULAR ASSIST DEVICES (LVAD)

LVAD is a useful class of devices used in patients with severe heart failure when the heart is no longer capable of pumping blood. The LVAD takes over the hearts pumping action until an artificial heart is available for implant. The LVAD is inserted in the chest cavity. This device simply moves blood from the left ventricle to the aorta and back through an air driven pump. One such LVAD is the IABP, used in the intensive care unit, cardiac catheterization laboratory, or the operating room. A local anesthetic is given over the artery at the top of the balloon that sits in the aorta and is hooked up to a large console that is continuously maintained by a specially trained technician. The console inflates the balloon during the time that heart is filling with blood for the next heart beat. The inflated balloon pumps the blood and then deflates when the heart is ready with the next heartbeat. Thus, enough blood flow is supplied to the organs of the body and some of the workload of the heart is reduced. This allows the heart to recover its strength. Although LVAD are currently used for short-term use, yet it is proposed that they will eventually replace artificial hearts and be used in permanent long-term implantation (23).

3.9 IOHEART

Unlike most organs in the body, the heart does not grow new cells to replace worn ones. As a result when heart cells die during an attack, this portion of the heart becomes dead tissue. The rest of the organ must work harder to compensate. This begins a cascade reaction towards heart failure. The best cure is a heart transplant. But the shortage of available organs as well as the dangers involved in this transplantation

process has motivated scientists to search for a way to regenerate heart tissue. Bioheart Inc., Fort Lauderdale-FL works on a "Myoblast technique."

Heart muscle cells were also considered, but these can fail due to the lack of oxygen. Hence heart muscle cells are not used for the regeneration. Instead cells from the thighs are used since they are more robust and are able to repair themselves (Figs. 23 and 24). A silver-dollar size portion of thigh muscle removed. The tissue is sent to a Bioheart laboratory, where it is put through an 18-step process to select out and multiply immature muscle cells, called myoblasts. Now the cellular composition is delivered to the area of the heart muscle that is damages due to infarction. For this a specialized system, Bioheart Myocath catheter system is used. Using this catheter, 10 to 30 pellets, each consisting of some 50 million cells, are injected in and around the damaged area of the heart.

The damaged heart muscle is now partially regenerated with healthy tissue. The implanted myoblast cells proliferate in a controlled manner growing in the oxygen deprived area. They are inherently resistant to ischemia and thrive only in an oxygen deprived infarct environment. A series of injections through the infarct area is then performed. After about 3–8 weeks, the autologous cells develop into functional contractile cells within the damaged myocardium. The initially scarred area now becomes functional myocardial tissue to a significant degree (25). The above technology developed by Bioheart is called as the Myocell™ (25). It is an autologous cell based product used for the treatment of Myocardial infarction and Congestive Heart Failure. It is currently in the clinical trial stage in US and Europe. Clinical trials began in Europe in May 2001. This technique is called myogenesis and is a part of study of tissue engineering. The technology developed by Bioheart Inc. involves cell transplantation that does not depend upon the availability of hearts for a transplant.

3.10 BIOPUMPS

3.10.1 PERISTALTIC PUMP

A Peristaltic pump (Fig. 25) consists of a tube and a roller system. It is a totally closed system with the tube carrying the material to be transported e.g. blood. The tube acts a valve as well as the transport mechanism. A roller compresses the tube in its forward motion. As a result the liquid tends to be pushed forward. These are completely self-priming, positive-displacement pumps with no check valves or components in the fluid stream. Since the system is noncontact fluid can be delivered without contamination and this is most important for biomedical applications. Because the tubing can be sterilized, the Peristaltic pump is the ideal system for sterile and other sensitive precision pumping situations. The peristaltic pumps come in a variety of designs and sometimes come with 2 rollers. The accuracy of a fill can be improved by increasing the number of rollers, which in turn increases the frequency of the pulse and reduces the impact of a single pulse. The pump head is typically made of polypropylene with silicone coated rollers. The pump heads are driven with precision stepper motors or DC motors. A micro controller usually controls the pumps and can this be programed to suit the application. Usually a digital thumb switch is provided to set the pump speeds. A 3 digit LED displays the current speed.

3.10.2 MAGNETIC BEARING PUMP

Foster Miller technologies are developing a high efficiency blood pump in association with the Cleveland Clinic foundation (Fig. 26). The pumps are based on the principle of magnetic levitation. This is a rotary pump designed for 5 liter/min and 100 mm Hg. It uses less than 8 W of input power. The magnetic suspension consists of a single active magnetic thrust bearing and a permanent-magnet radial bearing. The simple, radial flow impeller has no shroud or discharge stator blades. A secondary impeller provides a secondary blood flow path to minimize blood stagnation. Another design includes a flat motor. Two permanent-magnet rings, one on the stator and one on the rotor, support the pump in a plane. Three specially tuned electromagnets keep the pump stable in the magnetic field.

3.10.3 SYRINGE INFUSION PUMP

The Syringe infusion pump provides a uniform flow of fluid by precisely driving the plunger of a syringe down its barrel. It provides accurate and continuous flow rate for precise delivery of I.V. medication in critical medical care. **Harvard 1** has developed a syringe pump that is powered by Li-ion battery. The pump is lightweight and convenient to carry around in hospital from bed to bed (5). The pump is programmable and the program can be changed even while the pump is in operation. New bar code reading feature enables quick drug identification and setting of infusion rates with laser-reading of the drug's bar code (located on the syringe). This feature of the Harvard I represents a major milestone in the reduction of medication errors. Other special features of the pump include an advance "Near empty syringe" warning, LCD display screen, capacity to store up to 3000 drugs along with their safety limits and infusion ratings. Figure 27 shows the syringe pump developed by Harvard 1 medical technologies.

3.11 ROLE OF TAH IN THE TREATMENT OF END STAGE HEART FAILURE

Consistent estimates are that at least 50,000 to 100,000 patients yearly might benefit from mechanical cardiac assistance, but there has been no consistent estimate as to how many might be in need of a TAH. There is no evidence that imminently available technologies will dramatically decrease the need for mechanical assistance, or TAH in particular. However, as more mechanical support devices have become available, it is still uncertain how the correct device should be selected for each patient. The initial impression derived from postcardiotomy experience was that biventricular support would be required for a majority of patients, reported by some centers to exceed 50 percent. More recent experience indicates a lower need for biventricular support in chronic heart failure, which may reflect in part differences in chronic heart failure and acute postcardiotomy shock, and also the benefit of wider use of nitric oxide to reduce pulmonary vascular resistance The current need for biventricular support when mechanical assist devices are used in chronic heart failure is estimated to be 10 to 20 percent, with a slightly higher proportion of patients postcardiotomy and postinfarction who will be best served by replacement with a TAH.

Despite the prevalence of biventricular failure in patients with chronic heart failure, some, at least in the short-term, now demonstrate resolution of severe heart fail-

ure symptoms with left ventricular support alone. The long-term persistence of this improvement is not yet established. It is not known how many patients are considered ineligible for isolated left ventricular support due to predominant right ventricular compromise, intrinsic valve disease, small left ventricular cavity size, complex congenital anatomy and other factors. There is also insufficient information regarding the long-term success of LVAD placement in patients with ongoing ischemia.

3.11.1 LIMITATIONS OF VAD AND TAH

1. **Thromboembolism** in VAD and TAH recipients is thought to result from biomaterial surface- induced thrombus formation with systemic embolization. Considerable progress has been made in the development of materials with improved blood compatibility, but no materials developed to date are completely blood compatible and surface-induced thrombosis remains a real concern. Some devices employ a textured surface, which at first appears counterintuitive. However, while the roughness of such surfaces encourages fibrin deposition and platelet adhesion, the development of an adherent pseudointima so formed may be less prone to embolization than thrombi forming on smooth surfaces. The use of these textured surfaces has ranged from 8 to 35%. Also, use of these textured surfaces has decreased thromboembolism from approximately 20 to 2.7% (events per patients – month).
2. **Hemorrhage** occurs in about one third of patients receiving the TAH and remains a significant clinical problem. Bleeding is usually observed in the perioperative period or in the early postoperative period. Up to 50 percent of patients with VADs require reoperation for bleeding, although the operative use of the fibrinolytic inhibitor aprotinin may decrease both postoperative blood loss and the need for blood product transfusion. The causes of hemorrhage in TAH recipients are protean and are associated with preoperative coagulopathies due to hepatic dysfunction or poor nutritional status, cardiopulmonary bypass – induced thrombocytopenia or platelet dysfunction, and prolonged antibiotic therapy. This may be accentuated by the necessity of using antithrombotic therapy in some device recipients due to activation of both the coagulation cascade and platelets following exposure to the artificial surfaces of the device together with turbulent blood flow. In general, bleeding may be more of a clinical problem in patients who receive the TAH emergently following failed cardiac surgery with extended CPB or those supported for prolonged periods with extra corporeal membrane oxygenation. Conversely, the risk of bleeding is lower following shorter surgical implantation procedures. Bleeding may also be a significant problem during device explanation due to extensive adhesions. Hemorrhage remains a significant cause of death in recipients of both VAD's and TAH's. However, even if hemorrhage is not life threatening, it often necessitates blood transfusion. The transfused erythrocytes may be more prone to hemolysis by the device, and the increased hemolysis can lead to renal failure. The transfused granulocytes can also lead to alloimmunization that may be a clinical problem during subsequent heart transplantation.

3. **Infection** remains a major cause of death and morbidity in TAH/VAD recipients. Infection is seen in 25 to 48 percent of VAD recipients and approximately 37 percent of TAH recipients. Infection during VAD implantation has been associated with a decreased probability of survival when used as a bridge to transplantation. In a recent clinical study of the TAH, infections were most commonly noted approximately seven days post implantation, but infectious complications can be observed weeks to months after implantation. Most infectious complications are related to the device and often the use of percutaneous drivelines has been implicated. Other device-related infections included abdominal pocket infections; colonization of surface-induced thrombi; and direct bacterial colonization of the device lining materials. The principal pathogens associated with device infection have been Staphylococcus aureus, Staphylococcus epidermidis, Coagulase- negative staphylococci, Enterococcus fecalis, Enterococcus faecium, Serratia marcescens, and Candida species. Device recipients also may be susceptible to nosocomial infection due to long hospital stays, prolonged immobilization, and multiple intravascular catheters. In this regard, pneumonia and urinary tract infections have been reported. Recipients that receive a VAD after a failed cardiac transplant may be especially susceptible to infection due to their immunosuppressed state. Prevention of infection in TAH recipients may be multifactorial. Elimination of transcutaneous lines promises to decrease ascending infections. Decreased thromboembolism may decrease infection by preventing thrombi, which can be a source for bacterial colonization. Changes in patient management may also be useful to decrease infections and may include gut sterilization, avoidance of central and arterial lines, and use of oral prophylactic antibiotic therapy.

FIGURE 27 Syringe pump of Harvard 1 medical technologies (28).

4. **Multiple Organ Failure** has been reported to be the most common cause of death in a clinical TAH study. It was observed in 10 of 12 patients who died (83 percent). Multiple organ failure is most likely due to the selection of patients receiving a TAH. Most instances of multiple-organ failure are thought to

be due to poor perfusion and early end organ dysfunction prior to implantation in patients in cardiogenic shock for which the TAH was a last resort.

5. **Device Malfunction** is now relatively uncommon but is seen in approximately 4 percent of patients. The type of malfunction varies with the design of the device but is most often due to controller malfunctions. Occasional device failures have been due to valve dysfunction, driveline kinking and connector failure with loosening of the outflow conduit. TAH data from animal studies suggest that blood sac calcification may be a limiting factor to survival, but this may be a feature of using the rapidly growing calf as an animal model. Fit complications can be manifested due to compression of the inferior vena cava or pulmonary veins. Most current devices are designed for patients with a body surface area > 1.5 m^2. In addition to measurement of body surface area, it has been suggested that the anterior-posterior dimension of the thoracic cavity may also be a useful indicator of device fit. Further improvements in device size may allow employment of TAH devices in smaller women and in children.

3.12 COST OF A HEART TRANSPLANT

Heart transplants are costly procedures. The cost of a heart transplant may vary according to the hospital providing the transplant, the area of the country the operation takes place in, and the status of the patient's health. Many private health insurance companies cover many of the costs associated with heart transplants, including fees for the surgery, donor heart, medications and hospital stay. Medicare may also pay for heart transplants performed at approved facilities. Even with insurance, the patient may still be responsible for copayments, deductibles and nonmedical costs such as travel expenses. Many nonprofit organizations provide financial assistance for heart transplant recipients who do not have insurance, or who do not have enough money to cover their medical or travel costs. One may contact <www.transplantliving.org> for a list of these organizations. According to <transplantliving.org>, the average total cost of a single heart transplant in 2011 was $997,700 consting of: $47,200 for 30 days pretransplant, $80,400 for a donar heart, $634,300 for hospital transplant admission, $67,700 for physicians during the transplant, $137,800 for 180-days post-transplant admission, and $30,300 for immunosuppressant prescription medications.

More than 800,000 US patients die annually due to heart failure. About 50% die suddenly, with no chance for therapy. Heart transplantation is the best hope for rest of the patients, but only about 2,000 organs are available each year. And it is estimated that about 100,000 US patients can prolong their lives with a proven, reliable mechanical heart. This is a brief cost analysis of the potential market for the TAH: The complete heart replacement device can cost about $75,000 and procedural expenses can cost about $175,000.

3.13 FUTURE DEVELOPEMENTS OF THE ARTIFICIAL HEART

I. An Implantable artificial heart is being developed by Tohoku University (35): Novel mathematical models of hemolysis and blood coagulation from the viewpoint of nanoscale biofluid mechanics are being proposed. Furthermore,

by the use of VFP, a treatment of multiple organ failure by the blood flow distribution is being established. VFP has a very simple structure. It consists of a vibrating pipe with a valve. Due to the liquid inertia, resonance between the liquid and the gas, and the piston effect of the pipe, pumping effect can be recognized. VFP has received considerable attention because of the following advantages:

- Generating the stable oscillated flow.
- Self-priming function.
- Excellent controllability of the liquid flow.
- Decreasing the hemolysis by the use of jellyfish valve.
- High possibility of miniaturization for implantable artificial heart or for bio-MEMS.

II. Researchers at Carnegie-Mellon University and the Ford Motor Company announced successful prototype testing of a promizing new artificial heart powered by a diesel-fueled internal combustion engine: The heart, nicknamed the "Model H," consists of a compact 4-cylinder, 4-stroke compression-ignition engine driving a 4-chambered Teflon-coated bellows. The high power, high-efficiency engine is fed by a close-proximity high-density fuel reservoir, and exhaust is expelled through a set of muffled, microarticulated stacks designed to emerge discretely from just behind each of the ears. The engine is refueled through a dime-sized nozzle mounted just below the clavicle by means of a handy finger-pump-driven siphon. By making use of miniaturized combustion technologies, they have overcome the need for bulky external battery packs (35).

Based on the information in this chapter, we can observe: At an annual cost of $15 Billions, congestive heart disease is the most expensive treatment in the United States. More than 700,000 US residents die annually from heart failure, making it the number one cause of death in the United States as well as worldwide. Each year an estimated 400,000 patients are newly diagnosed with this clinical problem. An estimated 350,000 cases (i.e. 50% cases) die from sudden cardiac arrest as a result there is no time to address the patient with a cardiac assist device. But there are another 350,000 people whom have heart transplantation as a viable option for survival among some of the patients. Even though there are hundreds of thousands of patients that need a heart there are only roughly 2,300–2,500 cases a year that involve a patient donor. Therefore, there is a shortage in the supply of donor organs (i.e., hearts). This shortage demonstrates the need for an alternative transplantation namely Artificial Heart Transplantation.

Artificial Heart Development is a multidisciplinary research effort aimed at improving the design of existing artificial heart devices, and toward the development of the next generation of blood pumps. Computational Fluid Dynamics Computational Fluid Dynamics (CFD) is the application of state-of-the-art computational methods to calculate fluid flow behavior. Utilizing CFD as a tool for analyzing preexisting scenarios is advantageous because if offers insight, foresight, as well as efficiency for product design. A few TAH (Total Artificial Heart) currently in the market or in the prototype stage are functionally analyzed.

Artificial hearts serve different roles in each country. For example, Japan has significantly less heart transplant cases (i.e., 50 cases in 1999) as well as the *Law of Transplantation* has restricted many aspects of transplanting with donors. As a result the Japanese physicians tend to use the artificial devices as a permanent fixture. In the United States, physicians use the artificial heart as a bridge until a natural heart comes along. This is known as a *bridging device*. The emerging technology between Biomaterials/Biotechnology/Engineering and CFD, has created a new sense of hope for alternative artificial heart replacement. The mission of these fields is the prolongation of life in the 350,000 estimated people who need a heart replacement.

3.14 SUMMARY

The heart pumps blood to the human body. Artificial hearts are implanted in patients suffering from severe heart diseases. For the artificial heart system, we need to consider body fluids such as: Blood, intracellular fluids, extra cellular fluids, intravenous fluids and artificial (synthetic) blood. The use of anticoagulants (Heparin or Coumarin) is necessary in the implantation of an artificial organ. These act as blood thinners and prevent thromboembolism. Cardiovascular biomaterials are used to develop artificial heart valves, mechanical heart valves, pacemakers, vascular grafts, oxygenerators and cardiac assist systems (medical devices) like total artificial hearts, intraaortic balloon pumps etc. Some of the biomaterials used in medicine are metals, polymers ceramics and hydrogels. Biopumps can be peristaltic type, syringe type, or centrifugal type. Severe heart diseases can be treated by using the cell transfer technique developed by Bioheart Inc.. The Computational Fluid Dynamics (CFD) is employed to design a product and calculate fluid flow behavior. Utilizing CFD as a tool for analyzing preexisting scenarios is advantageous because if offers insight, foresight, as well as efficiency for product design.

KEYWORDS

- **AbioCor**
- **Anastomosing**
- **Angiography**
- **Angioplasty**
- **Anticoagulant**
- **Aorta**
- **Aortic valve**
- **Artificial heart**
- **Atria**
- **Atrium**
- **Axial pump**
- **Backflow**

- **Bicuspid aortic valve**
- **Bioheart**
- **Biological valve**
- **Biopump**
- **Blood clot**
- **Blood substitute**
- **BTR (Bridge to recovery)**
- **BTT (Bridge to transplantation)**
- **Cardiac assist devices**
- **Catheter**
- **Circulatory system**
- **Coronary artery**
- **Donor**
- **Electrocardiogram (EKG)**
- **Extra cellular fluids**
- **Extra corporeal**
- **Fibrillation**
- **Heart assist device**
- **Heart attack**
- **Hemodynamics**
- **Hemolysis**
- **Hetrotrophic**
- **Hypothermia**
- **Intra aortic balloon pump**
- **Intracellular fluid**
- **Intrathoracic**
- **Mechanical valve**
- **Mitral valve**
- **Myoblast**
- **Platelets**
- **Pulmonary**
- **Pulmonary autograft valves**
- **Pulmonary valve**
- **Regurgitation**
- **Right ventricular assist device (RVAD)**

- **Stenosis**
- **Systemic circulation**
- **Superior vena cava**
- **Thrombosis**
- **Thrombosis deep vein**
- **Thrombus**
- **Total artificial heart**
- **Tricuspid aortic valve**
- **United Network for Organ Sharing (UNOS)**
- **Ventricle (right and left)**
- **Ventricular assist device (VAD)**
- **Xenograft valve**

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APPENDIX I PULMONARY AND SYSTEMIC CIRCULATION (36).

The two principal fluid mechanical systems of the human body are the *cardiovascular* and p*ulmonary* systems. Cardiovascular system is a closed system in which blood circulated repeatedly within closed loops, whereas the flow of blood in the heart is called a CARDIAC CYCLE which is divided into seven following phases:

1. Atrial systole (Refer to the Figure for the cardiac cycle): A-V valves are open; Semi lunar valves are closed.

The P – wave of the electrocardiogram which represents electrical depolarization of the atria, initiates contraction of the atrial musculature. As the atria contract, the pressure within the atrial chambers increases so that a pressure gradient is generated across the open atrioventricular (AV) valves, thereby causing a rapid flow of blood into the ventricles. Retrograde atrial flow back into the vena cavae is impeded by venous return (inertial effect) and by the wave of contraction ("milking effect") throughout the atria. However, atrial contraction does produce a small increase in venous pressure that can be noted as the "a-wave" of the jugular pulse. Just following the peak of the a-wave is the *x*-descent. Atrial contraction normally accounts for only about 10% of left ventricular filling when a person is at rest because most of the ventricular filling occurs before the atria contract and therefore is passive. However, if heart rate is very high (e.g., during exercise), the atrial contraction may account for up to 40% of ventricular filling. This is sometimes referred to as the "atrial kick." Atrial contribution to ventricular filling therefore varies inversely with duration of ventricular diastole and directly with atrial contractility. After atrial contraction is complete, the atrial pressure begins to fall causing a pressure gradient reversal across the AV valves. This causes the valves to float upward (preposition) before closure.

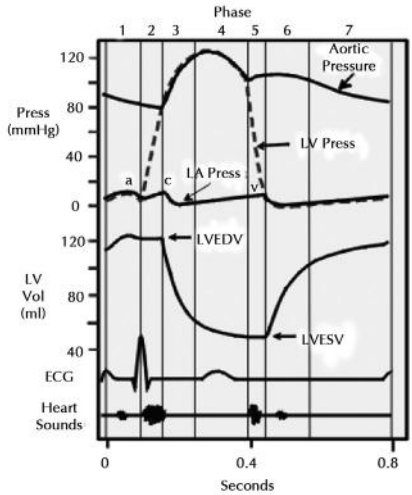


FIGURE 28A Cardiac cycle.

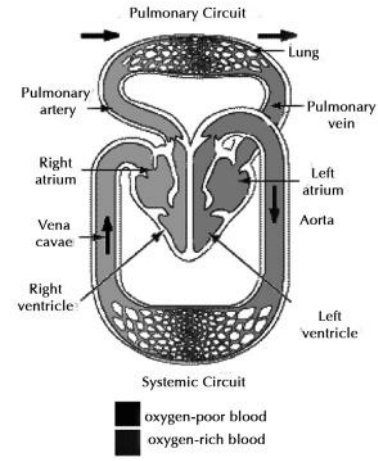


FIGURE 28B Circulatory system (Cardiac cycle).

Abbreviations:
Phase 1 Atrial contraction.
Phase 2 Isovolumetric contraction.
Phase 3 Rapid ejection.
Phase 4 Reduced ejection.
Phase 5 Isovolumetric relaxation.
Phase 6 Rapid ventricular filling.
Phase 7 Reduced ventricular filling.

LV Press: left ventricular pressure.
a = a-wave; ***c*** = *c*-wave; **v** = v-wave.
LVEDV: left ventricular end-diastolic volume.
LVESV: left ventricular end-systolic volume
LV Vol: left ventricular volume.

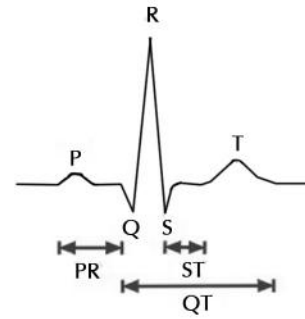


FIGURE 28C Cardiac cycle: Eletrocardiogram (ECG/EKG) (10)

At this time, the ventricular volumes are maximal. The ventricular end-diastolic volume (typically about 120 mL) constitutes the ventricular preload and is associated with end-diastolic pressures of 8–12 mmHg and 3–6 mmHg in the left and right ventricles, respectively. A heart sound is sometimes noted during atrial contraction (**Fourth Heart Sound, S_4**). This sound is caused by vibration of the ventricular wall during atrial contraction. Generally, it is noted when the ventricle compliance is reduced ("stiff" ventricle) as occurs in ventricular hypertrophy.

2. Isovolumetric Contraction (Refer to the Figure 28 for the cardiac cycle): All valves are closed.

The QRS complex of the ECG, which represents ventricular depolarization, initiates this phase of the cardiac cycle. As the ventricles depolarize, excitation-contraction coupling leads to myocyte contraction and the development of ventricular wall tension

and a rapid increase in intraventricular pressure. Early in this phase, the rate of pressure development becomes maximal. This is referred to as maximal ventricular dP/dt.

The abrupt rise in pressure causes the A-V valves to close as intraventricular pressure exceeds atrial pressure. Contractions of the papillary muscles with attached cordae tendinae prevent the A-V valve leaflets from bulging back into the atria and becoming incompetent (i.e., "leaky"). Closure of the A-V valves results in the First Heart Sound (S_1). This sound is normally split (~0.04 sec) because mitral valve closure precedes tricuspid closure.

During the time period between the closure of the AV valves and the opening of the semilunar valves, ventricular pressure rises rapidly without a change in ventricular volume (i.e., no ejection occurs). Contraction, therefore, is said to be "isovolumic" or "Isovolumetric." Individual myocyte contraction, however, is not necessarily isometric. Individual fibers contract isotonically (i.e., concentric, shortening contraction), while others contract isometrically (i.e., no change in length) or eccentrically (i.e., lengthening contraction). Therefore, ventricular chamber geometry changes considerably as the heart becomes more spheroid in shape; circumference increases and atrial base-to-apex length decreases.

Atrial pressures increase due to continued venous return and possible bulging of AV valves back into the atrial chambers. The "*c*-wave" noted in the jugular pulse is thought to occur due to increased right atrial pressure that results from bulging of tricuspid valve leaflets back into right atrium. Just after the peak of the *c*-wave is the x'-descent.

3. Rapid Ejection (Refer to the Figure 28 for the cardiac cycle): Aortic and pulmonic valves are open; AV valves remain closed.

When the intraventricular pressures exceed the pressures within the aorta and pulmonary artery, the aortic and pulmonic valves open and blood is ejected out of the ventricles. Blood is ejected because the total energy of the blood within the ventricle exceeds the total energy of blood within the aorta. In other words, there is an energy gradient to propel blood into the aorta and pulmonary artery. During this phase, ventricular pressure normally exceeds outflow tract pressure by only a few mmHg. Although blood flow across the valves is very high, the relatively large valve opening (i.e., low resistance) requires only on few mmHg of a pressure gradient to propel flow across the valve. Maximal outflow velocity is reached early in the ejection phase, and maximal (systolic) aortic and pulmonary artery pressures are achieved.

No heart sounds are ordinarily noted during ejection. The opening of healthy valves is silent. The presences of sounds during ejection (i.e., ejection murmurs) indicate valve disease or intracardiac shunts. Atrial pressure initially decreases, as the atrial base is pulled downward, expanding the atrial chamber. Blood continues to flow into the atria from their respective venous inflow tracts.

4. Reduced Ejection (Refer to the Figure 28 for the cardiac cycle): Aortic and pulmonic valves are open; AV valves remain closed.

Approximately 150–200 msec after the QRS, ventricular repolarization occurs (T-wave). This causes ventricular active tension to decrease and the rate of ejection (ventricular emptying) to fall. Ventricular pressure falls slightly below outflow tract pressure; however, outward flow still occurs due to kinetic (or inertial) energy of the blood. Atrial pressures gradually rise due to venous return.

5. Isovolumetric Relaxation (Refer to Figure 28 for the cardiac cycle): All Valves Closed. Refer to the cardiac cycle Figure.

As the ventricles continue to relax and intraventricular pressures fall, a point is reached when the total energy of blood within the ventricles is less than the energy of blood in the outflow tracts. When this occurs, the pressure reversal causes the aortic and pulmonic valves to abruptly close (aortic precedes pulmonic) causing the Second Heart Sound (S_2). Valve closure is associated with a small backflow of blood into the ventricles and a characteristic notch (incisura) in the aortic and pulmonary artery pressure tracings. The decline in aortic and pulmonary artery pressures is not abrupt as in the ventricles because of potential energy stored in vessel walls (see aortic compliance).

Ventricular pressures decrease; however, volumes remain constant because all valves are closed. The volume of blood that remains in a ventricle is called the end-systolic volume and is ~50 mL in the left ventricle. The difference between the end-diastolic volume and the end-systolic volume is ~70 mL and represents the stroke volume. Atrial pressures continue to rise due to venous return.

6. Rapid Ventricular Filling (Refer to Figure 28 for the cardiac cycle): A-V valves are open

When the ventricular pressures fall below atrial pressures, the AV valves open and ventricular filling begins. The ventricles continue to relax despite the inflow, which causes intraventricular pressure to continue to fall by a few additional mmHg. The opening of the AV valves causes a rapid fall in atrial pressures and a fall in the jugular pulse. The peak of the jugular pulse just before the valve opens is the v-wave. This is followed by the *y*-descent of the jugular pulse. If the AV valves are healthy, no prominent sounds will be heard during filling. When a Third Heart Sound (S_3) is audible, it may represent tensing of chordae tendinae and AV ring during ventricular relaxation and filling. This heart sound is normal in children; but is often pathological in adults and caused by ventricular dilation.

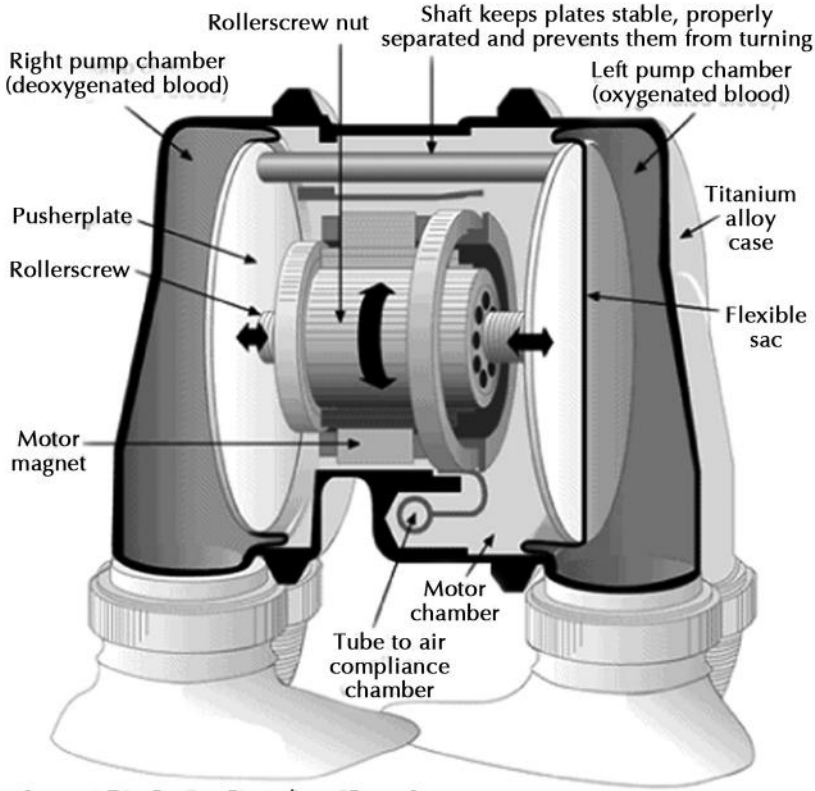
7. Reduced Ventricular Filling (Refer to Figure 28 for the Cardiac Cycle):

As the ventricles continue to fill with blood and expand, they become less compliant and the intraventricular pressures rise. This reduces the pressure gradient across the AV valves so that the rate of filling falls. Aortic pressure (and pulmonary arterial pressure) continues to fall during this period.

APPENDIX II PENN STATE TOTAL ARTIFICIAL HEART.

The Penn State total artificial heart

The Penn State total artificial heart (TAH) is driven by an electric motor. The motor turns a rollerscrew nut that pushes the rollerscrew sideways. The motor reverses polarity every four and one-half revolutions, and the rollerscrew is driven in the opposite direction. This back and forth mothion within the artificial heart duplicates the pulsing of a real heart.



Source: Dr. Gerson Rosenberg. Penn State

CHAPTER 4

BIOMATERIALS FOR AN ARTIFICIAL PACEMAKER[1,2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Jesus R. Bernardy, Yocli Comas, Jorge Esquilin, and Angel A. Hodge) under my guidance for the course on Mechanics of Materials, INGE 4011. Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, Mayaguez – PR – 00680, USA. For details contact at <goyalmegh@gmail.com> or visit at: http://www.ece.uprm.edu/~m_goyal/home.htm. I acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2]The numbers in parentheses refer to cited references in the bibliography.

4.1 INTRODUCTION

Our heart pumps blood to all cells of our body. This is vital, because the blood carries oxygen and nourishment to keep the cells alive and healthy. Natural pacemaker in the human heart governs a rhythmic physiological activity, especially the sinoatrial node that regulates heartbeat. Our heart beats because special cells in our heart (natural pacemaker) produce electrical impulses. These impulses cause the heart to contract and pump blood. The impulses travel from the pacemaker cells down certain electrical paths in the muscle walls, causing a contraction. As long as the electrical impulses flow down our heart's walls at regular intervals, our heart pumps at a rhythmic pace.

Sometimes, something interferes with the electrical impulses of natural pacemaker. When this happens, the natural pacemaker cannot do its job. Then an artificial pacemaker is installed in the human body. An artificial pacemaker is a medical device surgically implanted beneath the skin to provide a normal heartbeat by electrical stimulation of the heart muscle. The primary purpose of a pacemaker is to maintain an adequate heart rate, either because of the heart's native pacemaker is not fast enough, or there is a block in the heart's electrical conduction system. Today, more than 300,000 pacemakers are installed annually in USA. In this chapter, we shall discuss description of a pacemaker, milestones in the development of pacemakers, some examples of a pacemaker in the market, and biomaterials that are used for different components of a pacemaker.

4.2 DESCRIPTION OF AN ARTIFICIAL PACEMAKER

1. **A pulse generator** has a sealed lithium battery and an electronic circuitry package. The pulse generator produces electrical signals that make the heart beat. Many pulse generators also have the capability to receive and respond to signals that are sent by the heart itself.
2. **One or two wires (also called leads)** are insulated, flexible wires that conduct electrical signals to the heart from the pulse generator. The leads may also relay signals from the heart to the pulse generator. One end of the lead is attached to the pulse generator. The electrode end of the lead leads may be positioned in the atrium, ventricle, or both, depending on the condition requiring the pacemaker to be inserted. Pacemakers that pace either the right atrium or the right ventricle are called "single-chamber" pacemakers. Pacemakers that pace both the right atrium and right ventricle of the heart and require two pacing leads are called "dual-chamber" pacemakers. Older pacemakers sent out electrical signals at a constant rate, regardless of the heart's own rate. Pacemaker technology is now much more advanced. Today, pacemakers can "sense" when the heart's natural rate falls below the rate that has been programed into the pacemaker's circuitry (Fig. 1).
3. **An atrial arrhythmia** (an arrhythmia caused by a dysfunction of the sinus node or the development of another atrial pacemaker within the heart tissue that takes over the function of the sinus node) may be treated with an atrial permanent pacemaker with lead wire located in the atrium.

4. **A ventricular arrhythmia** (an arrhythmia caused by a dysfunction of the sinus node, an interruption in the conduction pathways, or the development of another pacemaker within the heart tissue that takes over the function of the sinus node) may be treated with a 'ventricular pacemaker with lead wire located in the ventricle.
5. It is possible to have **both atrial and ventricular arrhythmias**. There are pacemakers that have lead wires positioned in both the atrium and the ventricle. There may be one lead wire for each chamber, or one lead wire may be capable of sensing and pacing both chambers.
6. **An ICD** has a lead wire that is positioned in the ventricle, as it is used primarily for fast ventricular arrhythmias.

The Fig. 1 indicated components of a pacemaker. Table 1 shows typical specification of a pacemaker. Changing physiological needs that occur during running, swimming or gardening, for example, are met by the rate adaptive features of pacemaker. Furthermore, the latest generation of BIOTRONIK pacemakers can also react to mental changes. Everybody has experienced a sudden rise in pulse or blood pressure while watching an exciting film or if an unexpected event occurs. CLOSED LOOP Stimulation can adapt the pacing rate to both physical activity and emotional stress. BIOTRONIK's wide range of products allows the physician to appropriately diagnose and treat any rhythm disturbance. Due to extensive research, BIOTRONIK pacemakers today are not only technologically advanced but are also safer, smaller, lighter and more streamlined.

4.2.1 THE PACEMAKER AND SURROUNDINGS

1. Home appliances: CB radios, electric drills, electric blankets, electric shavers, ham radios, heating pads, metal detectors, microwave ovens, TV transmitters and remote control TV changers, in general, have **not** shown to damage pacemaker pulse generators, change pacing rates or totally inhibit pacemaker output.

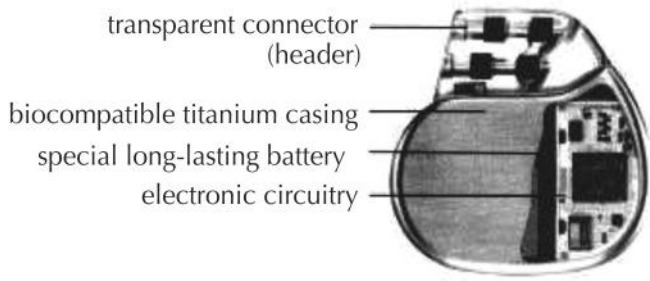


FIGURE 1 Schematic diagram of the pacemaker (23).

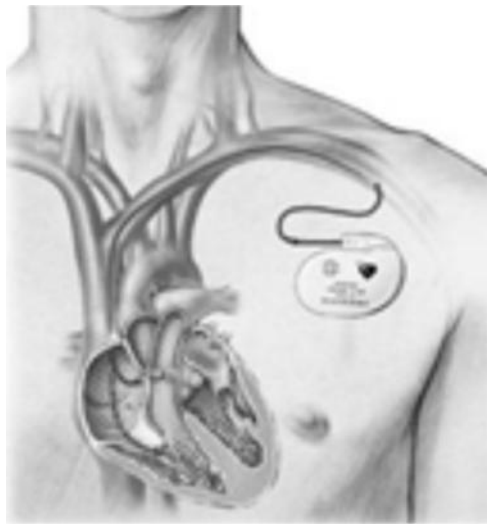


FIGURE 2 Location of the pacemaker near the heart.

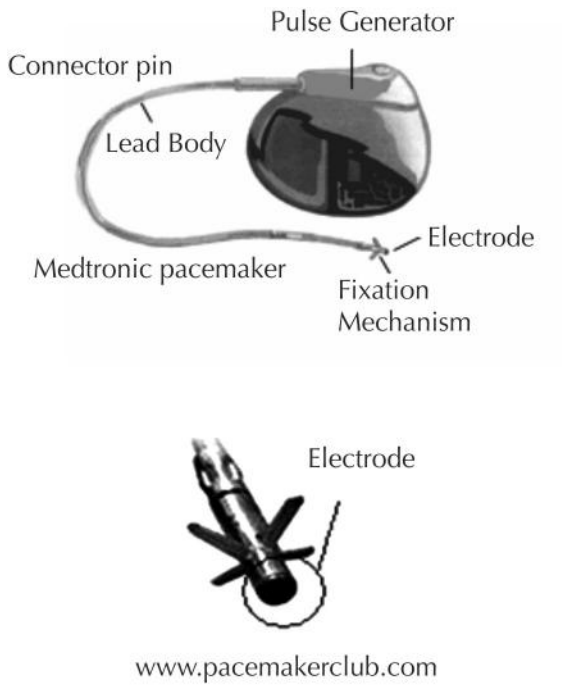


FIGURE 3 Components of a pacemaker (23, 30).

TABLE 1 Typical specifications of a pacemaker.

Pacemaker	
Dimensions	47 × 64 × 11.5 mm
Mass	38 g – 53 g
Case material	Titanium
Pulse Generator: material	
Battery chemistry	Encasing
Lithium-carbone	Titanium
monofluoride WG9086	
Lithium-iodine WG 8077	Upgrade from ceramics
Mercury	Epoxy resin with silicone rubber
Electrode: material	
Titanium.	
Silver alloyed with palladium.	
Platinum alloyed with iridium.	
Tungsten Carbide-Cobal.	
Lead wire body: material	
Injection molded.	
Polyether urethane.	
Polytetramethylene ether glycol and 1,4-butanediol	
Fixation Mechanism	
Nickel-cobalt alloy with silver core helix.	
Electrically active platinum-iridium helix.	
Titanium alloy screws.	

Several of these home devices have a remote potential to cause interference by occasionally inhibiting a single beat. However, most people can continue to use these devices without significant worry about damage or interference with their pacemakers. Power-generating equipment, arc welding equipment and powerful magnets (as in medical devices, heavy equipment or motors) can inhibit pulse generators. Patients who work with or near such equipment should know that the pacemakers may not work properly under these conditions.

2. Cell phones

Cell phones available in the United States (less than 3 watts) do not seem to damage pulse generators or affect how the pacemaker works. Technology is rapidly changing as the Federal Communications Commission (FCC) is making new frequencies available. Newer cell phones using these new frequencies might make pacemakers less reliable. A group of cell phone companies is studying that possibility.

3. The Pacemaker and the medical equipments

One should carry a wallet ID card, the doctors and dentists should be told if one has a pacemaker. Magnetic resonance imaging (MRI) uses a powerful magnet to produce images of internal organs and functions. The magnet can interrupt the pacing and inhibit the output of pacemakers. If MRI must be done, the pacemaker output in some models can be reprogramed. The possible risks and benefits should be discussed with the doctor before undergoing MRI scanning. Extracorporeal shock-wave lithotripsy (ESWL) is a noninvasive treatment that uses hydraulic shocks to dissolve kidney stones. This procedure is safe for most pacemaker patients, with some reprogramming of the pacing. One should be patients with certain kinds of pacemakers implanted in the abdomen should avoid ESWL. Specific case should be discussed with the doctor before and after the treatment. Radiofrequency (RF) ablation uses radio waves to manage a wide variety of arrhythmias. Recent studies of patients with implanted pacing systems measured the units before, during and after RF catheter ablation. These studies showed that most permanent pacemakers aren't adversely affected by radio frequencies during catheter ablation. A variety of changes in pacemaker can occur during and after the treatment. The doctor should carefully evaluate the pacing system after the procedure. Transcutaneous electrical nerve stimulation (TENS) is used to relieve acute or chronic pain. Most studies have shown that TENS rarely inhibits bipolar pacing. It may sometimes briefly inhibit unipolar pacing. This can be treated by reprogramming the pulse generator. Diagnostic radiation (such as X-ray screening) appears to have no effect on pacemaker pulse generators. However, therapeutic radiation (such as for treating cancerous tumors) may damage the pacemaker's circuits. The degree of damage is unpredictable and may vary with different systems. But the risk is significant and builds up as the radiation dose increases. The American Heart Association recommends that the pacemaker be shielded as much as possible, and moved if it lies directly in the radiation field. The electrocardiogram (ECG) should be monitored during the treatment, and the pulse generator should be tested often after and between radiation sessions. Dental equipment doesn't appear to affect pacemakers adversely. Some patients may feel an increase in pacing rates during dental drilling. Electroconvulsive therapy (such as for certain mental disorders) appears to be safe used in patients with pacemakers. Short-wave or microwave diathermy uses high-frequency, high-intensity signals. These may bypass the pacemaker's noise protection and interfere with or permanently damage the impulse generator.

4.2.2 THE IMPLANTATION OF A PACEMAKER

Due to today's technology, pacemaker implantation has become much easier and safer. This common procedure often takes less than an hour. Usually, the physician locally anesthetizes the region under the collarbone. Then the pacemaker lead is carefully inserted through a vein into the heart. Because blood vessels are not sensitive to pain, no extra anesthesia is needed. In general, *x*-ray monitoring is used for controlling the correct positioning of the lead within the right atrium or ventricle. Only after the functioning of the lead is tested will it be connected to the pacemaker. The pacemaker itself is implanted just under the skin in a small pocket below the collarbone (Fig. 4).

Finally, the physician closes the incision with stitches. The patient might have following general questions:

1. Can I go through airport security systems or antitheft detectors?

Yes. BIOTRONIK pacemakers are protected from the influence of external factors (for more information, please ask the physician). However, one must state that one has an implanted pacemaker, because the metal housing may set off the security alarm system. To be on the safe side, inform the airport personnel about the pacemaker and pass through the detector quickly.

2. **Do I feel the pacemaker working?**

No. The pacemaker functions at such a low level of electrical current that it only affects the heart and the surrounding tissue. However, should the patient experiences any symptoms (such as frequent hiccups), it is advizable to consult the physician.

3. How long does a pacemaker battery last?

The exact life for replacement depends on the pacemaker type, medical condition, lifestyle and other factors. The physician is the right person to tell.

4. What will happen when my pacemaker needs to be replaced?

The pacemaker is removed through minor surgery. The leads are left in the heart, provided they are functioning properly, and are connected to the new pacemaker. Usually a short hospital stay is necessary.

5. Will the leads also have to be replaced?

During pacemaker replacement, the doctor checks the leads to make sure that these are functioning properly. If these do not need replacement, then these will be simply connected to the new pace maker.

6. Will the pacemaker need adjusting after implantation?

Depending on the medical condition and lifestyle, a slight readjustment may be necessary.

7. Will the pacemaker still be able to provide work as the battery grows weaker?

Yes. The physician can determine how much battery life is lelt at the regular follow-up appointments.

8. How do a heart and a pacemaker react in the case of passing away?

A heart can only function when it is supplied with blood and energy. In the case of death, the small electrical impulses from the pacemaker will have no effect on the heart.

9. Can I use a mobile telephone?

Yes. One can use the mobile telephone safely, but some precautions should be taken: Check with the physician for specific situation. Be sure not to place the telephone near the pacemaker site (such as in the breast pocket). When using the cell phone, hold the receiver to the ear that is on the opposite side of the location of the pacemaker of a

body. Due to differences in telephone technology, the patient should check with the physician.

10. How often do I have to see my physician for follow-up visits?

The physician will determine the follow-up schedule.

11. Can I still use home electrical appliances such as microwaves, dryers, electric blankets, and massagers?

The normally functioning of home electrical appliances will not damage the pacemaker.

12. Will my body show allergic reactions to the pace maker materials?

Normally not. Pacemaker manufacturers use only highly biocompatible materials such as titanium or FDA proven plastics which do not react with bodily fluids.

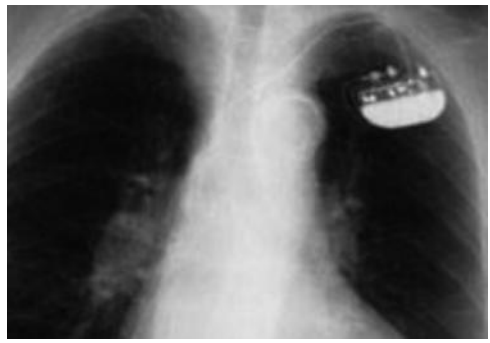


FIGURE 4 Frontal chest x-ray of dual chamber pacemaker (30).

4.2.3 MILESTONES IN THE DEVELOPMENT OF A PACEMAKER

4.2.3.1 THE FIFTIES AND EARLIER

Early external pacemakers: In 1899, J. A. McWilliam published his research in the British Medical Journal and indicated that application of an electrical impulse to the human heart in asystole caused a ventricular contraction. In cooperation with physicist Edgar H Booth at the University of Sydney, Dr Mark C Lidwell at Royal Prince Alfred Hospital –Sydney devised a portable apparatus (1926) which "plugged into a lighting point" and in which "One pole was applied to a skin pad soaked in strong salt solution" while the other pole "consisted of a needle insulated except at its point, and was plunged into the appropriate cardiac chamber." "The pacemaker rate was variable from about 80 to 120 pulses per minute." In 1928, a stillborn infant at Crown Street Women's Hospital – Sydney revived using their device. In 1932, American physiologist Albert Hyman, described his electro-mechanical instrument, powered by a spring-wound hand-cranked motor. Hyman referred to his invention as an "artificial pacemaker." Thus first artificial pacemaker was introduced. An external pacemaker was designed and built by the Canadian electrical engineer John Hopps in 1950 based upon observations by cardio-thoracic surgeon Wilfred Gordon Bigelow at Toronto General

Hospital. The vacuum tube technology was introduced to provide transcutaneous pacing. Thus pacemakers in the early 1950s were not totally implanted in the body. One end of the lead wire was implanted into the heart. The other end of the lead wire was connected to an external pacemaker that was AC powered. Mobility of the patient was limited to the length of extension cord. A power failure was a constant concern. The silicon transistor was developed and available commercially in 1956. It led to rapid development of practical cardiac pacemaking.

First battery-powered external pacemaker: In 1957, first transistorized, battery-powered, wearable pacemaker was developed. This gave patients mobility and eliminated concerns about a power failure. The research by Dr. William L. Weirich at the University of Minnesota, demonstrated the restoration of heart rate, cardiac output and mean aortic pressures in animal subjects with complete heart block through the use of a myocardial electrode. This effective control of postsurgical heart block proved to be a significant contribution to decreasing mortality of open-heart surgery in the late fifties. In 1958, an electrical engineer Jorge Reynolds Pombo constructed an external pacemaker weighing 45 kg and powered by a 12 volt auto battery, but connected to electrodes attached to the heart. His apparatus was successfully used to sustain a 70-year-old Gerardo Florez. In 1958, engineer Earl Bakken of Minnesota produced first wearable external pacemaker. This transistorized pacemaker, housed in a small plastic box, had controls to permit adjustment of pacing heart rate and output voltage and was connected to electrode leads which passed through the skin of the patient to terminate in electrodes attached to the surface of the myocardium of the heart. In 1958, a fully implantable pacemaker was a first clinical implantation in a human body at the Karolinska Institute in Solna – Sweden. This pacemaker was designed by Rune Elmqvist and surgeon Åke Senning and was connected to electrodes attached to the myocardium of the heart by thoracotomy. The device failed after three hours. A second device was then implanted which lasted for two days. Arne Larsson was the world's first implantable pacemaker patient and received 26 different pacemakers during his lifetime. In 1959, Furman demonstrated first temporary transvenous pacing with a catheter electrode inserted via the patient's basilic vein.

4.2.3.2 SIXTIES

First human implant of a totally implantable pacemaker: In February 1960, Swedish Elmqvist design was improved and implanted at the Casmu Hospital – Montevideo, Uruguay. The early Swedish-designed devices used rechargeable batteries, which were charged from the outside. The Wilson Greatbatch innovation was different from the earlier Swedish devices in using mercury battery as the energy source. The first patient who received Greatbatch device lived for 18 months. In 1963, pacemaker with capability to synchronize ventricular stimuli to atrial activation was introduced.

Advances in pacing leads: In the mid-1960s, "transvenous leads (TL) by Parsonnet in the USA" replaced earlier leads that were attached to the outer surface of the heart and TL under fluoroscopic guidance could be inserted through a vein leading to the heart. Pacemaker and lead implants could now be done without opening the chest cavity or using general anesthesia.

World's first "Demand mode" pacemaker: "Demand mode" pacemaker was introduced in the mid-1960s that provided pacing only when necessary. Earlier pacemakers continuously paced the heart at a set "fixed" rate..

4.2.3.3 SEVENTIES

Further advances: New designs of lead wires replaced earlier "smooth tip" leads. It prevented the lead from slipping out of place.

Extended battery life and new casing: In 1972, world's first Lithium iodide cell powered pacemaker was developed by Cardiac Pacemakers Inc., Minneapolis, USA. Thus introduction of a lithium iodide battery in 1975 extended the battery life (10+ years for some models) and replaced the mercury-zinc battery. Titanium casing was developed to enclose the battery and circuitry. Epoxy resin with silicone rubber previously encased the inner components. The new titanium casing (along with special filters) helped shield the components and reduced outside electromagnetic interference. Patients with these newly designed pacemakers could now safely use microwave ovens and other appliances and equipments in the home and office.

Electronic circuitry: A further impediment to reliability of the early devices was the diffusion of water vapor from the body fluids through the epoxy resin encapsulation affecting the electronic circuitry. The problem was overcome by encasing the pacemaker generator in an hermetically sealed titanium metal case by Telectronics of Australia (1969) and Cardiac Pacemakers Inc., (1972). The titanium metal encasing metal became the standard after 1972.

First programmable pacemaker: With the introduction of programmable pacemakers in the mid-1970s, pacemaker settings could be programed using radio-frequency signals. This eliminated the need for surgery when/if any pacemaker programming adjustments were necessary.

First dual-chamber pacing: The first programmable pacemaker that could sense and pace the upper (atrium) and lower (ventricle) chambers of the heart was introduced in the late 1970s. Using two leads, dual-chamber pacemakers maintained synchronized timing between the upper and lower chambers of the heart to ensure efficient blood flow.

4.2.3.4 EIGHTIES

First steroid-eluting lead: In the early 1980s, leads were made available that would deliver a steroid drug from the tip of the electrode to minimize inflammation of the heart wall.

TABLE 2 Specifications of a LD Pace-II DDD pacemaker (18).

Modes	**VVI, VVT, VOO, AAI, AAT, AAT, AOO, DDD, VDD**
Refractory periods	From 195 to 480 oms
Basic rate	From 36 to 120 min
AV delay	From 55 to 280 ms

TABLE 2 *(Continued)*

Modes	**VVI, VVT, VOO, AAI, AAT, AAT, AOO, DDD, VDD**
Amplitudes	From 0.7 to 5.5 V, unipolar/bipolar
Sensed AV delay	Shift of 5 to 40 oms
Pulse width	From 0.1 to 1.5 ms
Adaptive AV delay	on/off
Atrial sensitivity	From 0.5 to 4.0 mV unipolar/bipolar
UTR	From 36 to 140 min-[1]
Ventricular sensitivity	From 1.0 to 8.0 mV, unipolar/bipolar
UTR mode	Off, Wenckebach, Fixed Block
Blanking	From 39 to 63 ms
Hysteresis (single chamber)	From 0% to 20%
Non programmable parameters	
Independent upper rate limit	180 min-[1]
PVC response	The device reverts to DVI mode for a single cycle
End-of-service indicators	
EOL (End Of Life)	When the remaining capa-city of the battery is under 5%, the basic rate is de-creased by 10 min^{-1} and the ratio is incremented by one.
Latissimus Dorsi (LD) muscle pacing parameter	
Modes	VVI-LD, VVT-LD, VDD-LD, DDD-LD
Ratio	From 1:1 to 1:16
Output to muscle	Off, Ventricular pace and/or sense
Adaptive ratio	On/off, different ratios according to actual heart rate
Amplitudes	From 0.45 V to 7.5 V unipolar/bipolar
Adaptive train	On/off, different ratios according to actual heart rate
Pulse width	From 0.06 to 1.0 ms
Adaptive V-LD delay	On/off

TABLE 2 *(Continued)*

Pulse interval	From 16 to 133 ms
Work regiment	From 1 to 120 min
V-LD delay	From 2 to 350 ms
Magnet uses	No use, turn LD On/OFF, switch Ratio
Magnetic response	
Programed magnet response: no use	The presence of a magnet will have no effect.
Programed magnet response: off/on	The presence of a magnet will inhibit the muscle channel until the magnet is detected again.
Programed magnet response: switch ratio	The presence of a magnet will change the ratio to the programed night ratio. When the magnet is detected again, the ratio goes back to the programed Ratio.
Power source	
Battery chemistry	Liithium-Carbone monofluoride WG9086
Initial voltage	2.8 V (load 5 kohms)
Maximum available capacity	2.5 Ah
Physical characteristics	
Dimmensions	47 *x* 64 *x* 11.5 mm
Mass	53 g
Case material	Titanium
Cardiac connectors	IS-1
Muscle connectors	Special connectors
Service life: 8 years (10 yrs if the ventricle is sensed)	

The expected life of the generator: Stimulating 100% both, ventricule and lattissimus dorsi at 50 min-[1] with 2.5 V amplitude, pulse width of 0.488 ms, a burst of 6 pulse and ratio 1:4

Note: This is an example.

FIGURE 5 LD Pace- II (18).

Rate responsive pacing: Pacemaker with a "rate responsive" feature became available in the mid-1980s. A tiny crystal sensor inside the pacemaker detected the body movement and its signals adjusted the pacemaker rate up or down according to the wearer's activity.

4.2.3.5 NINETIES

Sophisticated devices: In the 1990s, pacemakers like microcomputers, were smaller than earlier devices (1/2 the size), and could last much longer. With the recent introduction of "mode switching," pacemaker can recognize an abnormally fast heart rate in the upper chamber of the heart and react by automatically changing the therapy provided by the pacemaker. This feature allowed the pacemaker to deliver the most appropriate pacing therapy.

Adjusting to the activity of each patient: In the late 1990's, pacemakers could mimic natural rhythm of the heart more accurately by adjusting the rhythm according to a person's activity level.

Storage of clinical data: Pacemakers can now collect information and store it until the next clinic visit. Some pacemakers also make follow-up easier by storing patient data directly into the memory of the pacemaker (such as name, diagnosis, doctor).

4.2.3.6 FUTURE DEVELOPMENTS

The significant contribution in the following years is note-worthy by the pioneers: Bob Anderson of Medtronic Minneapolis; J.G. Davies of St George's Hospital-London; B. Berkovits and Sheldon Thaler of American Optical; Geoffrey Wickham of Telectronics – Australia; Walter Keller of Cordis Corporation – Miami; Hans Thornander and Elmquist of in Sweden; Janwillem van den Berg of Holland and Anthony Adducci of Cardiac Pacemakers Inc. The developments were focused on:

1. Features and capabilities to increase the life of a battery;
2. Features to make follow-up visits easier and faster, including remote controlled evaluation of a pacemaker; and
3. Enhanced features to monitor the heart's activity and automatically change the therapy delivered by the pacemaker, with the objective to reduce number of follow-up visits to the physician.

4.2.4 SOME EXAMPLES OF PACEMAKER

Modern pacemakers are externally programmable and allow the cardiologist to select the optimum pacing modes for individual patients. Some combine a pacemaker and defibrillator in a single implantable device. Others have multiple electrodes stimulating differing positions within the heart to improve synchronization of the lower chambers (ventricles) of the heart. We shall now discuss following pacemakers that are available in the market (The author has no intention of not mentioning any model that might be superior).

1. **Implantable Pulse Generator** (Fig. 5 and Table 2), for cardiomyoplasty and aortomyosplasty surgical procedures, include: DDD pacemaker; flexible LD channel; work/rest periods, LD inhibition on PVC and UTR; programmable uses of the magnet; and friendly programmable.

2. **Apex Model SSI 3143** (Fig. 6 and Table 3): Coupled stimuli and temporary programming for tachycardia treatment; hysteresis; telemetry information of battery status; marker pulses; automatic access to Data Base; and statistics.
3. **External Pacemaker Model 196** (Fig. 7 and Table 4): Six programmable parameters; tachycardia treatment; and battery status indicator.
4. **Cardiac Resynchronization Therapy Pacemaker (CRTP, Fig. 6b)**: A cardiac resynchronization heart device sends tiny electrical pulses to the lower chambers of the heart so it can pump blood more efficiently. A CRT device sends small, undetectable electrical impulses to both lower chambers of the heart to help them beat together in a more synchronized pattern. This improves the ability of a heart to pump blood and oxygen to the body. The heart device itself is actually a tiny computer, plus a battery, contained in a small titanium metal case that is about the size of a pocket watch. It weighs about 3 ounces (84 grams). In addition to the heart device, insulated wires called leads are implanted: To carry information signals from the heart to the CRTP, and to carry electrical impulses to the heart. The third part of the implantable device system is a programer, an external computer located in your doctor's office or clinic that is used to program the heart device and retrieve information from the heart device that will assist the doctor in the heart failure treatment.

There are two types of implantable heart failure heart devices: a CRT pacemaker and a combination CRT pacemaker with defibrillation therapy (CRTP-D). Both of these devices help to coordinate the pumping action and improve blood flow. They can also speed up a heart that is beating too slowly. The CRTP-D also offers the ability to detect and treat dangerously fast heart rhythms, which some individuals with a damaged heart muscle may be at risk for developing. The doctor is the right person to determine which CRT device is appropriate for a perticular medical condition. The CRT devices by Medtronic for heart failure are Protecta XT CRT-D; Protecta CRT-D; Consulta CRT-D; Consulta CRT-P; Syncra CRT-P. Other CRT devices include just the pacing function (CRT-P) to treat slow heart rates and these are listed below:

1. **Conexus® Wireless Telemetry** allows remote monitoring of the device; device information can be collected and transmitted automatically, even while the patient is sleeping.
2. **OptiVol® Fluid Status Monitoring** monitors fluid build-up caused by worsening heart failure.
3. **PainFREE™ Therapy** delivers painless electrical pulses, potentially eliminating the need for a shock.
4. **Medtronic CareAlert® Notifications** has monitoring features that can signal the clinic if the heart condition or the device status changes
5. **Advanced Diagnostic Data** compiles long-term data to help manage device therapy and disease progression; includes Cardiac Compass® trends and the Heart Failure Management Report.
6. For more details, visit: <http://www.medtronic.com/patients/heart-failure/device/index.htm>. The detailed guidelines for cardiac pacing and CRT are given at:

< http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-cardiac-pacing-ES.pdf>.

FIGURE 6 (a) Apex model SSI 3143 (19). (b) Medtronic XT CRT-D device.

FIGURE 7 External Pacemaker model 196 (17).

TABLE 3 Specifications of an 'Apex SSI 3143′ pacemaker (19).

Programmable parameter	
Pacing modes	VVI, VVT, VVO, AAI, AAT, AOO, OFF
Basic pacing rates	From 30 to 120 min-[1]
Pulse widths	From 0.122 ms to 1.952 ms in steps of 0.122 ms
Refractory periods	From 203 to 438 ms in steps of 15.625 ms
Sensitivities	From 0.5 to 4.0 mV in steps of 0.5 mV
Hysteresis	From 0 to 20% in steps of 5%
Electrical configuration for pacing	Monopolar/Bipolar

TABLE 3 *(Continued)*

Programmable parameter	
Electrical configuration for sensing	Monopolar/Bipolar
Tachycardia treatment	
Temporary programming	From 30 to 400 min-[1]
Coupled Pacing Delay	395 ms, 410 ms, 426 ms, Off
Maximum Rate	From 60 a 150 min-[1]
Magnetic response	
Mode	VOO
Rate	At BOL: 80 ms reduction in pulse internal. At ERI: 80 ms. Increase in pulse interval.
End-of-service indicator	
ERI (elective replacement)	When the remaining capacity of the battery is between 4% and 8%, the pulse internal increase 80 ms when a magnet is applied.
EOL (End of life)	When the remaining capacity of the battery is under 4%, the pulse internal is increasedby 120 ms.
Power source	
Battery chemistry	Lithium-iodine WG 8077
Initial voltage	2.8 V
Maximum available capacity	1.66 A-hr
Physical characteristics	
Dimensions	47 X 55 X 8.5 mm
Mass	38 g
Case material	Titanium
Connectors	IS-1
Service life (11–12 years)	
The expected life of the generator depends on stimulating 100% at 70 min-[1] with 5 V amplitude and pulse width of 0.488 ms.	
Telemetry data	
Parameters	All programmable
Identification	Model and Serial Number
Battery condition	BOL OK, OK, ERI and EOL.
Statistics	Sensed operations and paced operations.
Protections	
Noise detection	When the pacemaker senses events with frequency exceeding 11 Hz, it changes to VOO mod

TABLE 4 Specifications of an external pacemaker model 196 (17).

Programmable parameter values	
Pacing modes	SSI, SOO, SST
Basic pacing rates	From 36 to 163 min-[1]
Pulse widths	From 0.170 to 1.850 ms, (12 values)
Pulse amplitudes	From 0.5 to 5.0 V in steps of 0.5 V, 8 V and 11 V
Refractory periods	250 and 350 ms
Sensitivities	From 0.5 to 4.0 mV in steps of 0.5 mV
Tachycardia treatment	
Temporary programming	Asynchronous stimulation using a rate 4 times greater then the basic rate. It is necessary to press a special button during operation.
Battery change indicator	
In normal operation, a green indicator lights following the cardiac rate. When the remaining charge of the batteries is less than 20%, the indicator turns red.	
Power source	
Type	2 alkaline AAA batteries
Nominal voltage	3 V
Service life (6 months)	
The expected life of the batteries depends on stimulating 100% at 70 min-[1] with 5 V amplitude and pulse width of 0.48 ms.	
Protections	
Noise detection	When the pacemaker senses events with frequency exceeding 11 Hz, it changes to VOO mode
Run away limit	The pacemaker includes an antirunaway circuit to avoid the generation of stimuli with a rate over 180 min-[1]. (except in temporary programming)
Trigger upper rate	117 min-[1]

4.3 MEDICAL DEVICE IDENTIFICATION CARD

Medical device identification card is provided free of charge by the manufacturer (See Fig. 8). The patient should carry the card at all times. This permanent ID card: Helps to keep records of a patient patient up-to-date; Identifies the patient as having an implanted medical device (pacemaker, defibrillator, or lead wire) in case of an emergency; Includes a toll free telephone number and email to contact the manufacturer; Helps in the treatment and care to the patient by the healthcare provider; and makes the travel easier for the patient.

4.4 BENEFITS AND RISKS OF A PACEMAKER

The benefits of a pacemaker are: By regulating the heart's rhythm, a pacemaker can often eliminate the symptoms of bradycardia. This means individuals often have more

energy and less shortness of breath. However, a pacemaker is not a cure. It will not prevent or stop heart disease, nor will it prevent heart attacks.

In addition to the general risks of surgery and the risks of anesthesia, pacemaker surgery presents its own risks. While less than 5% of patients experience problems after pacemaker surgery, it is important to be aware of potential complications. Gerald Naccarelli, M.D., Clinical Associate Director, at Penn State Hershey Heart and Vascular Institute, indicates: "Implantation of a pacemaker is a simple surgical procedure and infections can occur that can be treated with some antibiotics. The most devastating side effect of a pacemaker insertion is that an infection which would not heal if it is due to a generator and wire. There can be some bleeding at the wound where one sticks the vein. Sometimes the lead can move or even poke a hole in the heart. When the patient does not follow the instructions after the surgery, there is a concern about the movement of lead wires that are screwed in into the heart muscle. Life-threatening complications of pacemaker implantation are rare." The risks due to implantation of a pacemaker are summarized below:

- Allergic reaction to the dye or anesthesia used during the procedure.
- Bruizing at the site of placement (this is an expected effect of surgery).
- Nerve damage at the incision site.
- Damage to the tissues or blood vessels around the heart or the incision site.
- Pneumothorax (collapsed lung).
- Faulty pacemaker that does not function as intended after the surgery (very rare).
- Swelling, bruizing or bleeding at the generator site, especially if the patient is taking blood thinners.
- Faulty lead wires that connect the pacemaker to the heart (very rare).
- Lead wires that become dislodged after surgery due to activity or poor placement.
- Puncture of your heart muscle, which can lead to bleeding into the lining (pericardium) of the heart and may require emergency medical care.

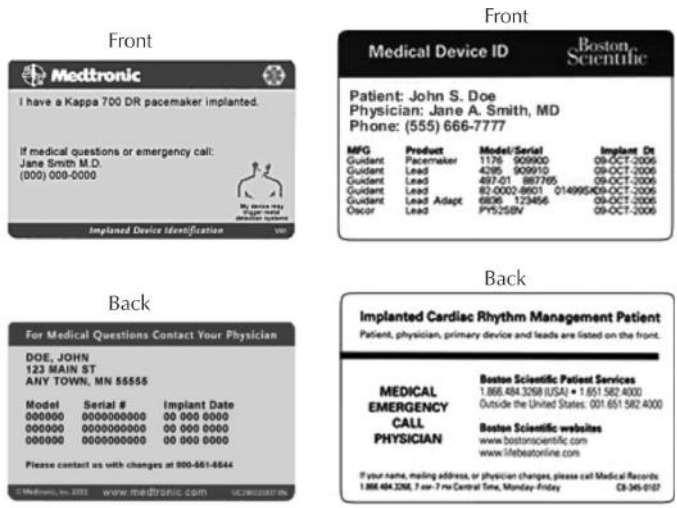


FIGURE 8 Pacemaker identification card: Left – <medtronic.com>, and Right – <bostonscientific.com>.

4.5 TRENDS IN CARDIAC PACEMAKER BATTERIES

The lithium/iodine-polyvinylpyridine battery by W. Greatbatch, first implanted in 1972, has become the choice of a power source for the cardiac pacemaker. Over the last 20 years, improvements in cell chemistry, cell design, and modeling of cell performance have been made. Battery cells today exhibit an energy density over three times as great as cells produced in 1972. Well over 2 million pacemakers have been implanted with this chemistry, and the system has exhibited excellent reliability.

Usually the battery of a pacemaker lasts for 5 to 10 years. It takes several months over a period of several months to run down. At each follow-up visit the doctor will check the battery and once the period is over, another pacemaker will be inserted.

4.6 MATERIAL CHARACTERISTICS FOR EACH COMPONENT OF PACEMAKER

1. Casing of a Pacemaker

- Battery: Lithium-carbone; Lithium-iodide; and mercury.
- Electronic circuitry: Converts electrical energy to electrical signals and controls timing of the delivery of signals.

Common casing materials are:

- Titanium**:** High modulus of elasticity; high resistance to corrosion; high durability; strong; noncorrosive; and not degraded.
- Upgrade from ceramics and epoxy resin with silicone rubber.

2. Electrode

- Located at tip of lead.
- Delivers electrical energy from pacemaker to heart and information from heart back to pacemaker.

Common electrode materials are:

- Titanium: High modulus of elasticity; high resistance to corrosion; and high durability.
- Platinum-iridium: Stronger than most steels; used in steroid-eluting leads.
- May be coated with iridium oxide: Prevents nonconductive layers from forming; and reduces local inflammation.
- Stainless steal, silver and cobalt alloys.

3. Lead body

- Requirements: Flexible; durable; noncorrosive; and good electrical conductor

Materials of lead body are:

- Insulated with silicone rubber or polyurethane
- Polyurethanes: High strength; enables thinner lead to be used; offers greater lead flexibility; and very low coefficient of friction when wet.
- Silicone rubber: Not degraded by metal ion-induced oxidation.

4. Steroid eluting leads

- Electrode emits steroid when exposed to body fluids to suppress inflammatory response of heart wall; and reduces energy requirements of pacemaker.

- Platinum-iridium porous electrode contains silicone rubber matrix.
- Silicone rubber matrix contains steroid.
- Dexamethasone sodium phosphate: Soluble Polyethylene glycol or mannitol capsule placed on electrode tip to facilitate passage of fixation mechanism.

5. Fixation Mechanism

- Holds the tip of the lead (electrode) in place in the heart.
- Materials currently used:
  - Nickel-cobalt alloy with silver core helix.
  - Electrically active platinum-iridium helix.
  - Titanium alloy screws.

6. Connector pin

- Inserted into connector block.
- Permits continuous communication between pacemaker and lead.
- Injection molded of polyether urethane.
- Composed of polytetramethylene ether glycol and 1, 4-butanediol.

4.7 PROPERTIES OF BIOMATERIALS

Titanium is used for casing, electrode and fixation mechanism. In 1946, Kroll showed that titanium could be produced commercially by reducing titanium tetrachloride with magnesium. This method is largely used for producing the metal today. Titanium, it has a low density, good strength, is easily fabricated, and has excellent corrosion resistance. It is ductile only when it is free of oxygen. Titanium is as strong as steel, but is 45% lighter. It is 60% heavier than aluminum, but is twice as strong. Tables 5 and 6 indicate physical and chemical properties of titanium.

Tables 7 and 8 show properties of cobalt alloys. Table 9 indicates properties of polyurethane that is used for lead body and connector. Steriod eluting leads can be made of polyethylene glycol (Table 10) and silicone rubber sheet (Table 11). Table 12 indicates properties of silver that is used for electrodes. Stainless steel 316LS can be used as medical implant alloy (Table 13). Physical and mechanical properties of biomaterials for a pacemaker are compared in Table 14.

4.8 RESEARCH ADVANCES

There are limitations and risks in the success of an artificial pacemaker: Electrode fracture or damage to insulation, infection, reoperations for battery exchange and venous thrombosis. Can such a medical device be implanted in the premature newborn baby? Therefore, there is a scope for a gene therapy to develop a biological heart (BH). In the beginning of twenty-first century, Arjang Ruhparwar and his group at Hannover Medical School in Germany were successful in the development of a BH using transplanted fetal heart muscle cells. They were able to create a BH by injectiing an "Adenylate Cyclase" gene into the heart muscle.

TABLE 5 Characteristics of titanium (24).

Property	Value	Property	Value
Atomic number	22	Atomic weight	47.90
Density	4.50 g/cm3	Atomic	10.64
at 293 K		volume	cm3/mol
Physical states			
Melting point	1933 K	Boiling point	3558 K
Heat of fusion	15.450	Heat of	421.00
	kJ/mol	Vaporization	kJ/mol
Oxidation and electrons			
Shells	2,8,10,2	Electron configuration	(Ar)
			3d2–4 s2
Minimum oxidation number	-1	Maximum oxidation number	4
Minimum common oxidation number	0	Maximum common oxidation number	4
Conductivity			
Thermal conductivity	21.9 J/m-sec-deg	Electrical conductivity	23.81–1/mohm-cm

TABLE 6 Mechanical properties of titanium (24).

Mechanical properties			
Property	**Metric**	**English**	**Comments**
Density	4.51 g/cc	0.163 lb/in³	Typical
Ultimate Tensile Strength	725 MPa	105 ksi	Typical
Tensile Strength (Yield)	570 MPa	82.7	Typical
		ksi	0.2% proof stress
Elongation	16 %	16 %	Typical
at Break			
Modulus of Elasticity	105–120 GPa	15200	Typical
		– 17400 ksi	
Fatigue Strength	360 MPa	52200 psi	Limit
Thermal properties			
Beta Transus	960°C	1760°F	—

TABLE 7 Properties of a cobalt: (electrode, fixation mechanism) (24).

Physical properties		
	Metric	English
Density	8.8 g/cc	0.318 lb/in³
Mechanical properties		
Hardness, Brinell	125	125
Hardness, Vickers	253	253
Tensile Strength, Yield	225 MPa	33 ksi
Modulus of Elasticity	211 GPa	30600 ksi
Poisson's Ratio	0.32	0.32
Shear Modulus	82.6 GPa	12000 ksi
Electrical properties		
Electrical Resistivity ohm-cm		6.24e-006
Magnetic Permeability	Max 245	Max 245
Magnetic Permeability	68	68
Thermal properties		
CTE, linear 20°C	12.5 µm/m-°C	6.94 µin/in-°F
CTE, linear 250°C	14.2 µm/m-°C	7.89 µin/in-°F
Heat Capacity	0.44 J/g-°C	0.105 BTU/lb-°F
Thermal Conductivity	69.21 W/m-K	480 BTU-in/hr-ft²—°F

TABLE 8A Properties of a Co-Ni alloy: (electrode, fixation mechanism) (24).

Component, weight %		
B	2	—
C	0.6	—
Co	46.9	—
Cr	16.2	—
Fe	1.3	—
Ni	23.5	—
Si	1.9	—

TABLE 8A *(Continued)*

W	7.6	—
	Metric	**English**
Density	9.06 g/cc	0.327 lb/in³
	Mechanical properties	
Hardness, Rockwell C	41–46	41–46
	WALLEX 50 – Cobalt-Nickel alloy	
	Component, weight %	
B	3.4	—
C	0.8	—
Co	45.05	—
Cr	19	—
Fe	1	—
Ni	18	—
Si	2.75	—
W	10	—
Density	9.1 g/cc	0.329 lb/in³
	Mechanical properties	
Hardness, Rockwell C	56–61	56–61

TABLE 8B Properties of a Co-Ni alloy: (electrode, fixation mechanism) (24).

WALLEX 60 – Cobalt-Nickel Alloy		
Component	**Wt. %**	
B	2.3	
C	2.3	
Co	36.25	
Cr	12.35	
Fe	0.65	
Ni	9	
Si	1.75	
W	35.4	
Density	11.9 g/cc	0.43 lb/in³
Mechanical Properties		
Hardness, Rockwell C	Min 58	Min 58

TABLE 9 Properties of a polyurethane: (lead body, connector pin) (24).

	Metric	English
Density	1.09–1.12 g/cc	0.0394–0.0405 lb/in³
Linear Mold Shrinkage	0.006 cm/cm	0.006 in/in
Melt	11-	11 –
Flow	26 g/10 min	26 g/10 min
Mechanical Properties		
Hardness Shore A	92	92
Tensile Strength, Ultimate	16–35.2 MPa	2320–5110 psi
Tensile Strength, Yield	12–35.2 MPa	1740–5110 psi
Tensile Modulus	0.0827–0.745 GPa	12–108 ksi
Heat Capacity	1.5 J/g-°C	0.359 BTU/lb-°F
Thermal Conductivity	0.19 W/m-K	1.32 BTU-in/hr-ft²—°F

TABLE 10 Properties of a polyethylene glycol: steroid eluting leads (24).

	Metric	English	Comments
Specific Gravity	1.22 g/cc	0.0441 lb/in³	ASTM D792
Linear Mold Shrinkage	0.005–0.006 cm/cm	0.005–0.006 in/in	ASTM D955
Mechanical properties			
Tensile Strength, Ultimate	31 MPa	4500 psi	ASTM D638
Elongation at Break	Min 10 %	Min 10 %	ASTM D638
Modulus of Elasticity	1.38 GPa	200 ksi	ASTM D638
Flexural Modulus	1.38 GPa	200 ksi	ASTM D790
Electrical properties			
Electrical Resistivity	1e+009–1e+010 ohm-cm	1e+009–1e+010 ohm-cm	ASTM D257

TABLE 11 Properties of silicone rubber sheet: **lead body, steroid eluting leads** (24).

Specification:	Test Method	Units	Test Results
Specific Gravity	ASTM D792	g/cm3	1.2
Hardness	ASTM D2240	Shore A	50+-5
Tensile Strength	JIS K6301	kfg/cm2	100
Elongation	JIS K6301	%	390
Breakdown Voltage	UL94HB	KV	24
Volume Resistively	UL94HB	cm	1 *x* 1015

TABLE 12 Properties of silver: electrode (24).

Property	Metric	English
Density	10.491 g/cc	0.379 lb/in³
Mechanical properties		
Hardness, Vickers	25	25
Tensile Strength, Ultimate	140 MPa	20 ksi
Modulus of Elasticity	76 GPa	11000 ksi
Poisson's Ratio	0.37	0.37
Shear Modulus	32 GPa	4640 ksi
Electrical properties		
Electrical Resistivity	1.55e-006 ohm-cm	1.55e-006 ohm-cm
Thermal properties		
Heat of Fusion	105 J/g	45.2 BTU/lb
CTE, linear 20°C	19.6 µm/m-°C	10.9 µin/in-°F
CTE, linear 250°C	19.9 µm/m-°C	11.1 µin/in-°F
Thermal properties		
Heat Capacity	0.234 J/g-°C	0.0559 BTU/lb-°F
Thermal Conductivity	419 W/m-K	2910 BTU-in/hr-ft²—°F
Optical properties		
Emissivity (0–1)	0.055	0.055
Reflection Coefficient, Visible (0–1)	0.9	0.9

TABLE 13 Properties of a stainless steel 316LS: Medical implant alloy (24).

	Metric	English
Density	7.95 g/cc	0.287 lb/in³
Mechanical properties		
Hardness, Rockwell B	88	88
Tensile Strength, Ultimate	586 MPa	85000 psi
Tensile Strength, Yield, 0.2% offset	434 MPa	62900 psi
Elongation at Break	57 %	57 %
Reduction of Area	88 %	88 %
Electrical properties		
Electrical Resistivity	7.4e-005 ohm-cm	7.4e-005 ohm-cm

TABLE 13 *(Continued)*

	Metric	English
	Thermal properties	
CTE, linear 20°C	18.5 µm/m-°C	10.3 µin/in-°F
CTE, linear 250°C	18.5 µm/m-°C	10.3 µin/in-°F
CTE, linear 500°C	18.5 µm/m-°C	10.3 µin/in-°F
Heat Capacity	0.5 J/g-°C	0.12 BTU/lb-°F

TABLE 14 Composition of mechanical properties of biomaterials.

Property	units	STAINLESS STEEL 316	Titanium	Cobalt	Silver
Tensile Strength Ultimate	MPa	579	725	420	140
Tensile Strength Yield	MPa	290	570	225	269
Elongation at Break	%	55	16	45	2
Modulus of Elasticity	GPa	193	105 – 120	—	—
Density	g/cc	8.08	4.51	8.8	10.5
Poisson's Ratio	g/cc	0.305	0.33	0.32	0.37
Shear Modulus	GPa	10.7	90	82.6	32

In 2002, Eduardo Marban and his group at Johns Hopkins University published first successful gene-therapeutic approach towards the generation of pacemaking activity using a guinea pig model. On July 16 of 2009, an article titled, "Adult Human Stem Cells as a Platform for Gene Therapy: Fabricating a Biological Pacemaker by Michael R Rosen, Peter R Brink, Ira S Cohen, and Richard B Robinson at Center for Molecular Therapeutics – Department of Pharmacology – Columbia University, New York – 10032 – USA" was published in <discoverymedicine.com>. They indicated that "Many people carry electronic pacemakers and these devices work quite well. However, they do not automatically adjust heart rates in response to special circumstances, like exercise or emotion. Stem cells isolated from adult bone marrow can be genetically engineered to behave like the heart's own natural pacemaker. These stem cells can grow and integrate with native surrounding heart muscle cells, allowing the heart to react more naturally to the surroundings." They used "the sinoatrial node (the primary BH in the heart)" as a model to fabricate a BH. The sinoatrial node is a specialized tissue, integrated electrically and structurally into the heart muscle, which generates a regular rhythm rate that varies in response to the physiological and emotional demands of the body. The sympathetic (excitatory) and parasympathetic (inhibitory) limbs of the autonomic nervous system modulate the regular rhythm of a human heart. Researchers at Columbia University see a revolutionary future for BH in medicine.

4.9 SUMMARY

The pacemaker is used in the human body to regulate rhythm disorders. This chapter presents biomechanics and biomaterials of the pacemaker. The heart is basically a hollow muscle with four chambers – the two atria (this is the upper chamber) and the two ventricles (this is the lower chambers). The heart is divided into a right and a left side and is responsible for pumping blood throughout the body. In order for the blood to be collected and pumped out, the heart depends on tiny electrical impulses passed from the upper chambers to the lower chambers. These impulses usually start at the sinus node, which is also known as the natural pacemaker. Thus, the sinus node is the one that coordinates contraction and allows the heart to beat rhythmically. Impulses are then carried from the upper chambers into the lower chambers, which then contract. This contraction is called a heartbeat. Disease or age-related processes can disturb the natural heart rhythm. Very common disorders are problems in the conduction system or possible blockage of the pathways. As a result, the heart may beat irregularly and/or too slowly. In this case, our body – especially under physical stress – will supply insufficient oxygen, causing dizziness, feelings of weakness or tiredness. This kind of rhythm disorders is termed as bradycardia. In the case of AV block, the conduction of the electrical signals between the sinus node (in the atrium) and the AV node (in the ventricle) can be partially or totally blocked. With a total AV block, the electrical conduction between the atrium and the ventricle is interrupted. So a different center of the heart will generate a very slow, auxiliary rhythm to ensure life-saving function. In either one of these situations, or in other, even less common cases, the heart can be assisted through the use of an artificial pacemaker.

KEYWORDS

- **Antineo plastic agent**
- **Artificial pacemaker**
- **Atria**
- **Atrium**
- **Biocompatible**
- **Blood**
- **Bradycardia**
- **Carbamate**
- **Carbamic acid**
- **Chamber**
- **Diathermy**
- **Ductile**
- **Electrical impulse**
- **Electroconvulsive**
- **Electrode**

- **Electromagnetic wave**
- **Electron**
- **Electronic circuitry**
- **Frequency**
- **Heart chamber**
- **Heart muscle**
- **Hysteresis**
- **Leakage**
- **Ligament**
- **Magnetic field**
- **Microwave**
- **Muscle**
- **Node**
- **Nourishment**
- **Pacemaker**
- **Pulse**
- **Pulse generator**
- **Rhythm**
- **Sinus node**
- **Spinal cord**
- **Strain**
- **Tachycardias**
- **Tensible**
- **Tensile**
- **Urethane**
- **Ventricle**
- **Wave length**

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19. http://www.ccc.com.uy/ssi3143.htm
20. http://www.chfpatients.com/implants/pacemaker.htm
21. http://www.healthyhearts.com/pacemaker.htm
22. http://www.hrt.org/pages/cwgcp991120r2.html
23. http://www.lokit.com/polyurethane.htm
24. http://www.matweb.com/index.asp?ckck=1
25. http://www.medicinenet.com/Pacemaker/pace1.htm
26. http://www.medtronic.com/
27. http://www.naspe.org/ep-history/topics-in_depth/fiandra.asp#present
28. http://www.pacemakerclub.com/
29. http://www.rampro.net/info7.htm
30. http://www.tickerfixers.com/pacemaker%20cxr.htm
31. http://www.uihealthcare.com/news/pacemaker/about.html

APPENDIX I

LIST OF USEFUL SITES (HTTP://WWW.PACEMAKERCLUB.COM/PUBLIC/JPAGE (1) P/WEBLINKS/CONTENT.DO)

I. Pacemaker and implantable cardioverter defibrillator (ICD) manufacturers: The leading pacemaker and (ICD) manufacturers provide patient-oriented information on their websites so one can learn more about condition of a patient and device.

- Medtronic – www.medtronic.com
- St. Jude Medical – www.sjm.com
- Boston Scientific/Guidant – www.bostonscientific.com
- Vitatron – www.vitatron.com
- Biotronik – www.biotronik.com
- ELA/Sorin – www.sorin.com
- Wilson Greatbatch (batteries) – www.greatbatch.com
- Baikal – imzcorp.com/en/info/article_pacemaker_2.html
- CCC –
- Medico –

- Pacetronix – www.pacetronix.com
- Elestim-Cardio – www.elestim-cardio.ru/en
- Cardioelectronica – www.cardioelectronica.com

II. Pacemaker and ICD information sites: These websites provide helpful information on ICD, pacemakers and cardiac arrhythmias.

- American Heart Association – heart.org
- Arrhythmia Technologies Institute – www.arrhythmiatech.com
- Biophan Technologies – www.biophan.com
- Cardiac Pacing Links by Wolfgang Scheibelhofer
- Food and Drug Administration (FDA) – www.fda.gov
- Implantable Device Reference Guide
- Heart Authority – www.heartauthority.com
- Heartbeat International – www.heartbeatintl.org
- Heart Point – www.heartpoint.com/pacerintro.html
- Heart Rhythm Society – www.hrsonline.org
- LifeBeat Online – www.lifebeatonline.com
- Medical Device Link – www.devicelink.com
- Wikipedia (about pacemakers)
- Wikipedia (about ICDs)

III.Support and emotional healing: Other support groups and organizations assist the patients with emotional stress related with a cardiac device.

- Atrial Fibrillation Support Group – Afibsupport.com
- Cardiac Athletes – www.cardiacathletes.org
- CHF Patients – www.chfpatients.com
- Children's Heart Federation – www.childrens-heart-fed.com
- Hope With Heart (summer camps) – www.hopewithheart.com
- Implantable.com – www.implantable.com
- Non Compaction Cardiomyopathy
- Med Help International – www.medhelp.org
- Mended Hearts – www.mendedhearts.org
- Wired4Life – www.wired4life.net
- STARS-US – www.stars-us.org
- The Zapper – www.zaplife.org
- Young Paced Hearts – www.youngpacedhearts.com

IV. Living healthy and safely: Sites to help implantable device recipients live healthy and safely.

- Ask the Dietitan – www.dietitian.com
- Dietary Guidelines for Americans – www.health.gov/dietaryguidelines
- Healthy Heart Market – healthyheartmarket.com
- Med Scope Alert Systems – www.medscope.org
- Med Tees – medtees.com
- Medical Alert System – www.liferesponseusa.com
- Quit Smoking – www.cdc.gov

- Social Security Disability Resource Center – www.ssdrc.com
- SoftTouch (seatbelt & bra comfort) – www.aboutsofttouch.com
- Wellness Quest – www.wellnessquest.com

IV. Monitoring service providers: Companies that monitor pacemakers and ICDs.

- Cardiac Monitoring Center – www.pacercheck.com
- First-Call Medical – www.fcminc.com/pacer.html
- Mednet Healthcare – www.mednethealth.net

V. Heart diseases and conditions: List of organizations that provide information on the heart and associated conditions.

- Canadian Adult Congenital Heart Network – www.cachnet.org
- Congenital Heart Information Network – tchin.org
- Encyclopedia of Surgery – www.surgeryencyclopedia.com
- Health4Care – www.health4care.com
- Heart Failure Society of America – www.hfsa.org
- SADS Foundation – www.sads.org.au
- WebMD – www.webmd.com

CHAPTER 5

BIOMATERIALS FOR CAROTID STENTING[1,2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Tatiana Ramirez Pacheco, Abraham Santiago Rivera and Gretchen M. Torres) for the course on Mechanics of Materials – 1. Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com≥ or visit at: <http://www.ece.uprm.edu/~m_goyal/home.htm>. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2]The numbers in parentheses refer to cited references in the bibliography.

5.1 INTRODUCTION

In medicine, the procedure of carotid stenting has arisen from trials of stenting to do a simple balloon angioplasty in the carotid arteries. This procedure consists of fitting a stent inside a carotid artery to increase the flow of blood blocked by plaques. After this a ballon-tipped catheter is inserted to inflate the artery and reopen it. The stents act as a scaffold to prevent the artery from collapsing or being closed by plaque after procedure. Biomaterials for artificial organs inside our body must be biocompatible should not cause reactions or side effects in the human body. The ballon-tipped catheter and stents need to be wear resistant and elastic to fulfill the purpose. Threfore, the biomaterials for a stent should be selected after a thorough study.

This chapter will discuss biomaterials for carotid stenting. The impetus for carotid stenting has arisen principally from trials of stenting with balloon angioplasty versus simple balloon angioplasty in the coronary arteries, which have consistently demonstrated a persistent benefit in event-free survival at one year and a lower rate of repeat angioplasty. The advantages of stent placement over simple angioplasty include avoiding plaque dislodgment, intimal dissection, elastic vessel recoil, and late restenosis. Despite the fact that it is unknown whether these benefits apply to the carotid circulation, endovascular carotid revascularization is now most commonly performed with stents (3).

The carotid arteries develop atherosclerosis in the same manner as the coronary arteries in the heart. Atherosclerosis is a buildup of cholesterol and other materials inside the inner lining of the arteries. These deposits lead to the formation of plaques, which protrude from the inner lining of the arteries and then obstruct blood flow to organs such as the heart and the brain. The blood flow to the brain diminishes as the carotid arteries narrow. If the artery becomes completely blocked or if a piece of the plaque breaks loose travels to smaller arteries in the brain and blocks them, a stroke can result. A stroke (or "brain attack") is similar to a heart attack. When brain cells (neurons) are deprived of oxygen and glucose carried to them by blood, a stroke occurs. Oxygen and glucose are essential for neurons to function and survive (13).

There are some risks that can be linked to atherosclerosis. Examples are: high cholesterol, smoking, a family history and hypertension. Typically, a few years later than the coronary arteries become diseased; the carotid arteries become diseased too. People with heart diseases have a higher probability of having carotid disease. The following tests on the patient are conducted to check if the candidate will benefit from carotid stenting procedure:

- Carotid Angiogram (arteriogram) – this is an invasive and accurate method to determine if the patient will benefit from stenting or surgery.
- Carotid Ultrasound.
- Computed Tomography (CT) of the brain without contrast.
- Medical examination with ausctultation (listening) of the carotid arteries with a stethoscope.

5.1.1 CATEGORIES OF DISEASE APPROPRIATE FOR CAROTID STENTING

- The etiology of carotid bifurcation disease can be categorized into atherosclerotic and non atherosclerotic processes, the former presenting much more frequently than the latter in clinical practice. The non atherosclerotic is caused by

carotid bifurcation and may be further subdivided into inflammatory problems, such as early postendarterectomy restenosis, Takaysu's arteritis, postendarterectomy intimal hyperplasia, and carotid stenosis occurring as a result of spontaneous dissections. It is assumed that the short-term results of carotid stenting would be best in non atherosclerotic disease, especially early recurrent lesions after endarterectomy, because the lesions are, by and large, smooth. As such, the potential for embolization is theoretically lower than that associated with complex atherosclerotic lesions. Clearly, the treatment of patients with the more esoteric causes of carotid stenosis is complicated, based on little more than anecdotal experience and, as such, should involve consultative input from a broad spectrum of specialists, including rheumatologists, hematologists, and vascular medicine practitioners.

- In patients with atherosclerotic disease, the risk of carotid stenting is correlated with the extent of the atherosclerotic process. The patients with significant intracranial disease and patients with diffuse disease involving the aortic arch and common carotid vessels should be viewed with caution. The heavily calcified, tortuous vessel is one fraught with difficulty, and the use of alternate treatment modalities should be strongly entertained. It is important to consider that patients with displacement of the arch vessels to the right side of the chest comprise a group for which technical difficulties may be expected. With the demonstration of the efficacy of coronary angioplasty and stenting, there is presently great interest in percutaneous treatment for carotid disease (Fig. 2).
- The large number of patients with suitable carotid lesions sparked interest by industry, and, despite a national "noncoverage" policy for carotid angioplasty by the Health Care Financing Administration (now Center for Medicare and Medicaid Services). Carotid stenting became one of the most widely discussed and hotly debated topics in the late 1990s. Interventional cardiologists, well versed in percutaneous angioplasty, were quick to embrace the new technology. Vascular surgeons, by contrast, viewed carotid angioplasty a crude and an unproved threat to the meticulous procedure of carotid endarterectomy: one of the mainstays of contemporary peripheral vascular surgical practice. With neurologists and neurosurgeons in the middle, a conflict ensued, the resolution of which could be achieved only through the completion of well-controlled comparisons of the two treatment modalities (13).

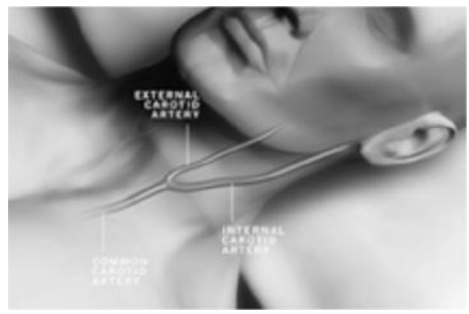

FIGURE 1 Carotid artery diagram (1).

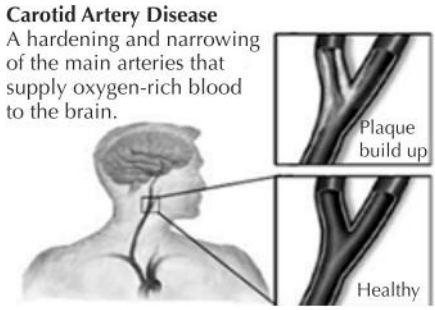

FIGURE 2 Carotid artery diseases (15).

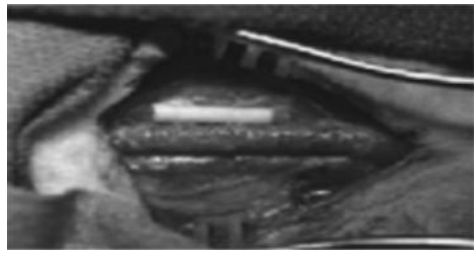

FIGURE 3 Carotid stent implantation (11).

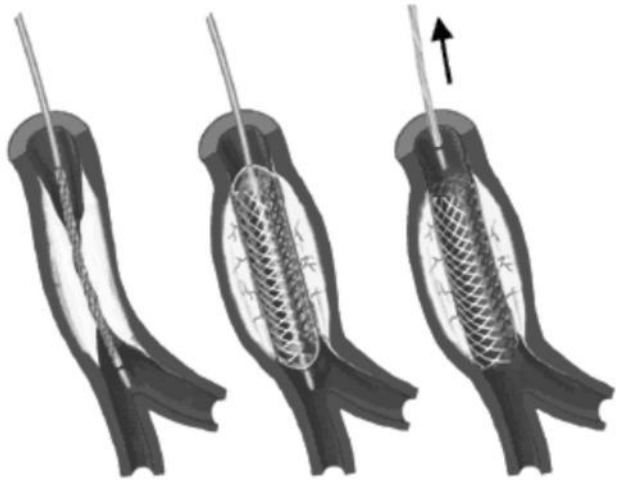

FIGURE 4 Carotid stenting in a patient with a symptomatic right internal carotid lesion (9).

5.2 CAROTID STENT AND ANGIOPLASTY PROCEDURE (13)

a. What Does Happen During the Procedure?

1. An intravenous (IV) line is inserted in the arm so that medications and fluids can be administered during the procedure

2. Then electrodes (flat, small, sticky patches) are placed in the chest. The electrodes are attached to an electrocardiograph monitor.
3. A blood pressure cuff is placed on the arm to monitor the blood pressure.
4. A small clip, attached to a pulse oximeter, is placed on the finder to monitor the oxygen level of the blood. The heart rate, blood pressure and oxygen level of the blood are closely monitored during and immediately after the examination
5. It is important that the patient is awake and conscious during the entire procedure. He or she is not be given a sedative. The doctor and nurses frequently check on the patient during the procedure.
6. A Foley catheter may be inserted to drain urine to reduce the risk of bleeding from the groin site. The catheter is removed after the procedure, when the patient is able to walk.
7. The nurse cleans the skin at the site where the catheter will be inserted (arm and groin). The site is covered with sterile drapes. The patient is instructed to keep the arms and hands down on the sides, under the sterile cover. This helps to prevent infection.
8. The doctor uses a local anesthetic to numb the site. A plastic introducer sheath (a short, hollow tube through which the catheter is placed) is inserted though a blood vessel in the arm or groin. A catheter is inserted through the sheath and threaded to the arteries of the neck (left and right carotid artery).
9. The lights are dimmed and a small amount of "contrast material" is injected through the catheters into the arteries when the catheter is placed. The contrast material outlines the vessels that provide circulation to the brain.
10. The patient feels hot or flushed for several seconds when the contrast material is injected. This is normal and will go away in a few seconds.
11. The doctor and nurses will try to keep the patient comfortable as during the procedure.
12. The X-ray camera is used to take photographs of the arteries of the head and neck. The patient may be asked to hold the breath or turn the head in different directions while the X-rays are taken.
13. If a blockage is seen, a specially designed catheter, with an umbrella tip is placed over the guide wire and directed to the area of narrowing in the carotid artery. Once in place, a small balloon tip is inflated for a few seconds to dilate the artery. Then, the stent (a small stainless steel mesh tube that acts as a scaffold to provide support inside the artery) is placed in the artery and opens to fit the size of the artery. Tiny filters are used to capture any particles that are released and prevent them from going to the brain and causing a stroke. The catheter is removed and the stent stays in place permanently. After several weeks, the artery heals around the stent (13).
14. If the patient feels an allergic reaction (like itching or tightness in the throat), loss of feeling in the arms and legs, a headache or any other symptoms, he or she should tell the doctor. The procedure of carotid stenting and angiography takes about two hours.

b. After the Procedure

1. The catheters and sheath are removed from the groin. Pressure aid is placed on the leg artery. The patient will need to lie flat and keep the leg straight for three to six hours to prevent bleeding. A pressure dressing will be applied tightly on the groin. The nurse will check the bandage regularly. Call the nurse if there is a bleeding (have a wet, warm sensation) or if the toes begin to tingle or feel numb. The patient will need to be on bed rest for several hours.
2. The patient may have some tenderness at the site of catheter insertion.
3. The patient will need to drink plenty of liquids to clear the contrast material from the body. He or she may feel the need to urinate more frequently. This is normal.
4. After the stent is placed, the patient will spend one night in the hospital for monitoring (12).

c. After Hospitalization Care

1. Follow check up visit will include a physical examination, neurological evaluation and diagnostic studies, such as carotid ultrasound.
2. The doctor will discuss wound care, diet, and when one can return to normal activities.
3. One will be asked to take the blood pressure two times a day for 30 days post stent procedure and record the values on a blood pressure record. One will require to purchase a blood pressure monitoring equipment.
4. One will be prescribed medications to prevent blood clots from forming for at least six months after the procedure.

d. Possible Complications and Risks

1. Slight risk of stroke because of a loose piece of plaque or a blood clot blocking an artery during or immediately following surgery.
2. Abrupt closure of the artery after surgery;
3. Restenosis (the reoccurrence of plaque buildup) that occurs after a stent has been placed in the carotid artery, preventing future endarterectomy; or
4. Short periods of reduced blood pressure and heart rate that may occur, which is treated with medications.
5. Perhaps the most serious potential risks involved with carotid stenting are the risk of a disrupted plaque particle that breaks free from the site, called an embolism, and blocks an artery in the brain, causing a stroke. These risks are minimized using small filters called embolic protection devices in conjunction with angioplasty and stenting. Hyper perfusion, or the sudden increased blood flow through apreviously blocked carotid artery and into the arteries of the brain, may occur after stenting, and can cause a hemorrhagic stroke (9).

In Figs. 4 and 5, the reader can observe: In part (A) the preintervention angiogram, demonstrating a critical stenosis; In part (B) one can observe the postintervention, without residual stenosis; In part © we can observe how the preintervention baseline intracranial angiogram is demonstrating poor filling of the anterior cerebral vessels from the right-sided injection; Finally in part (D) we can observe the outcome after stenting, in where the anterior cerebral circulation is now well visualized (arrow) (12).

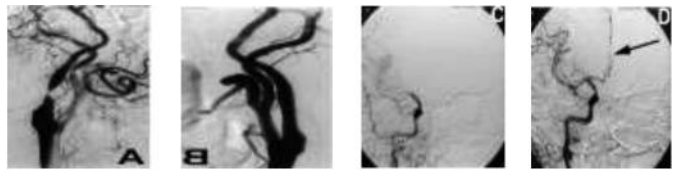

FIGURE 5 Carotid stenting in a patient with a symptomatic right internal carotid lesion (21).

5.3 PAST, PRESENT AND FUTURE OF BIOMATERIALS

In bioengineering, different materials are used. All materials have a set of properties, principles and characteristics that these should be understood by bioengineers. Engineers should also have knowledge on the characteristics and properties of tissues, organisms and devices. The biomaterials are evolutionized day to day. In the past, there was a growing understanding of the need of materials for implants and artificial applications. It was until the late 50's that implanted materials and devices evolved. As bioengineering developed from electrical engineering/instrumentation to mechanical engineering/biomechanics activities, there was an increasing realization of the need to understand the principles and tools of modern metallurgy, ceramics and polymer materials. After this, applications and activities in the area of artificial internal organs as the internal cardiovascular repair, swiftly developed-first vascular grafts and later artificial heart valves, ventricular assist devices and total artificial hearts. Later the development of orthopedic implants led to the concern of biocompatibility of materials and corrosion. Thus a speciality of development of material design evolved (29).

Before the intensive study of the biocompatibility and the existence of biomaterials, resistant 316 stainless steel was used. Later the use of the more highly corrosion resistant cobalt (Co)-chromium (Cr)-molybdenum (Mo) and related alloys were used as biomaterials. After the discovery of the use of Titanium as a biomaterial, there was an early recognition of the importance of the biocompatibility, stability, and biodegradation of materials for implant and related bioengineering applications. Then ceramics were acknowledged as a potentially biocompatible and bioactive material and accepted that the mineral matrix of bone could be duplicated by the used of vitro ceramic material preparation process. At present the concern with tissue reaction, tissue compatibility, corrosion, blood compatibility and related biointeraction and biodegradation processes have led to the emphasizing and growing interest on the surface chemistry, engineering of biomaterials and physics used in medical implants. The rapid development and maturing fields of surface chemistry, modification and characterization are applied to the development and research to new biomaterials. These results in the ability to modify, characterize, apply and engineer surface and interface technologies to improve biomaterials. Also the study of molecular biology and strong cell biology components of the materials is a growing interest. Therefore the design and development of new and novel materials using modern molecular biology methods is on the way.

In the future, the development of new biomaterial will require a more careful, broad and forward-looking study. Medicine and bioengineering will apply the information

in the new genomes to comprehend the repair, development of tissue and organs and the regeneration to largely minimize the use and necessity of artificial devices. As the knowledge of biology keeps augmenting, the use of biomaterials will be for repairing and regenerating of tissues and organs instead of constructing artificial devices. It is best to prolong our organs and tissues (29).

5.4 RESEARCH ADVANCES

A POTENTIAL LIMITATIONS OF PAST STANDARD THERAPY FOR CAROTID DISEASE

Carotid endarterectomy is a well proven intervention for carotid disease. The results of numerous clinical trials have documented its safety and efficacy; hence, it is a standard care for patients with severely stenotic extracranial lesions, whether the patient is symptomatic or not. Nevertheless, the excellent results achieved with the procedure appear to be dependent on the medical history of the patient. Relatively healthy patients do very well with open surgical repair of carotid lesions. The treatment of medically compromised patients, however, is associated with a much greater risk of complications, as illustrated in a review of more than 3000 patients undergoing carotid endarterectomy at the Cleveland Clinic Foundation between 1988 and 1998. In this analysis, the risk of the composite end point of stroke, myocardial infarction, or death was quite satisfactory in patients who did not manifest one of four classes of baseline comorbidity (coronary artery disease requiring intervention, congestive heart failure, chronic lung disease, and renal insufficiency). The risk of perioperative morbidity and mortality was substantial, however, when patients exhibited one or more baseline comorbid conditions. Specifically, the risk of perioperative death was elevated by a factor of more than 5, stroke or myocardial infarction each by a factor of 2, and the composite end point of death, stroke, or myocardial infarction by a factor of almost 3 (22).

B RESULTS OF PRESENT TRIALS OF CAROTID STENTING (21)

Comparative outcome analysis will resolve issues of safety and efficacy of carotid stenting versus carotid endarterectomy. A broad spectrum of carotid stenting trials exists. Most have been registry-type analyzes, involving prospective entry of a series of consecutively treated patients without a comparison group. These trials include single-center studies, in which the investigator served as the sponsor, as well as a variety of corporate-sponsored trials with such diverse acronyms as ACCULINK for revascularization of carotids in high-risk patients (ARCHeR); Boston Scientific/EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH); Carotid Artery Revascularization Using the Boston Scientific EPI FilterWire EX and the EndoTex NexStent (CABERNET); Evaluation of the Medtronic AVE Self Expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis (MAVErIC); and Stenting of High risk patients Extracranial Lesions Trial with Emboli Removal (SHELTER). Most of these registries were designed to evaluate patients thought to be at high risk for standard carotid endarterectomy and organized in an effort to gain approval for the stent and/or embolic protection device. The U.S. Food and Drug

Administration (FDA) has demonstrated some flexibility in the consideration of device approval based on high-risk registries rather than randomized studies.

The largest carotid stent registry is the global registry organized by Mark and Michael Wholey. At the time of the latest publication from this registry, more than 5000 patients had been entered from 36 centers worldwide. Although the data suffer from the limitations inherent in any registry based on unmonitored, investigator-completed questionnaires and nonstandardized follow-up protocols, the results were truly exceptional. Within 30 days of the procedure, transient ischemic attacks occurred in 2.8% of the patients and minor and major stroke in 4.2%. The 30-day mortality rate was 0.9%, with a combined stroke/death rate of 5.1%. The rate of restenosis was extremely low, being evident in only 3.5% of patients at one year, and only 1.4% of patients experienced neurologic symptoms 1–12 months following the procedure.

There have been several randomized trials of carotid stenting versus endarterectomy. Various studies are ongoing in Europe. A study sponsored by Schneider (now part of Boston Scientific Corporation, Natick, MA) compared placement of the wall stent without cerebral embolic protection with carotid endarterectomy. The results of stenting in this trial, if anything, were worse than those with endarterectomy. However, a number of sites had little stenting experience at the time of their participation in the study. A subgroup analysis documented poor results in these low volume centers (21).

The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is designed to compare the outcome of carotid stenting with that of endarterectomy in a patient population similar to that of the NASCET trial—in other words, in patients at relatively low risk for complications after carotid darterectomy. The trial employs the AccuLink™ stent and the AccuNet™ filter (Guidant Corporation, Menlo Park- CA). The goal is to randomize approximately 2500 patients in this NIH- and Guidant-sponsored trial. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial has been completed, and results were reported at the 2002 American Heart Association Meeting.

SAPPHIRE study composed of a randomized portion and a registry portion. Patients deemed suitable for either stenting or endarterectomy were randomized. Patients who were thought unsuitable for endarterectomy on the basis of severe medical comorbidities or anatomic considerations were entered into a stenting registry. Lastly, a small number of patients who were considered to be unsuitable for stenting, usually on the basis of anatomic criteria, were entered into a surgical registry. The study, which was sponsored by Cordis/Johnson and Johnson, used the Precise™ stent and AngioGuard filter (Cordis, Johnson and Johnson, Warren, NJ). The 30-day outcome data in the randomized portion of the SAPPHIRE study demonstrated significant benefit of stenting over endarterectomy for the composite end point of stroke, myocardial infarction, or death. Although not assured, it is expected that this finding will persist beyond the 30-day time point. If so, SAPPHIRE will be the study that gains FDA approval for the procedure of carotid stenting in general and the Precise/AngioGuard system in particular for the subgroup of patients at high risk for standard carotid endarterectomy (21).

C THE FUTURE OF CAROTID STENTING

The refinement of stent technology continues to evolve. In the days to come, in addition to providing mechanical support to the vessel wall, stents will also carry agents (chemicals or genetic material). These so-called "smart stents" will deliver these agents directly to the site of angioplasty. Stents capable of releasing radioactivity have shown both beneficial effects and important shortcomings in early clinical trials, emphasizing the need for further research. Stents made of bio-degradable material, which disintegrate in two years after placement are also under evaluation. Although recurrence of narrowing is an issue, with proper patient selection, more than 85 percent of patients undergoing stent placement can be expected to have a very favorable outcome without the need for any further procedure or bypass surgery. Future developments in stent technology are likely to allow more patients to undergo angioplasty successfully (25).

5.5 DESIGN REQUIREMENTS OF STENTS

A NONLINEAR FEA FOR DESIGN BIOMEDICAL STENTS

Modern angioplasty procedure can unclog the partially obstructed arteries and often is safe/viable alternative to critical bypass heart surgery. To open arteries or veins where deposits restrict blood flow, cardiologists use a catheter with a balloon tip, carefully guided into position and inflated to push the obstructions. Then a *cylindrical sleeve-type* device called a *stent* is inserted into the blood vessel. It is necessary to keep the walls from collapsing under spasmodic contractions and leave the vessel open for continuous blood flow.

During this secondary procedure, the balloon-tipped catheter with the stent mounted at the end is maneuvered to the site where the blockage is removed. The pressurized balloon expands the stent against the vessel wall, deflates, and exits with the catheter. This procedure leaves the stent permanently secured in the vessel. Stents are used frequently throughout the human body, but the most critical applications are in coronary arteries. Stents open pathways in vessels and supply blood directly to the heart muscle. A major challenge for designers of coronary stents is to make them smaller, more flexible, and stronger than types used in the rest of the body. These stents must sustain cyclical loads during normal heart activity.

Several different types of stents are used, but the barrel-type stent is best suited to coronary operations. It is fabricated from thin-walled stainless-steel alloy tubes with intricate patterns in wall openings, frequently made by laser machining. The pattern in these openings provides the necessary flexibility to pass through the vessel while attached to the catheter. It must expand from two to four times the initial stent diameter and have enough strength to maintain the vessel opening throughout the lifetime. Stainless-steel alloys are usually preferred for stents, and proven to be fully biocompatible for long-term implants in the human body (20).

New FDA submittal requirements on stent characteristics and performance push for reliable testing. Biomedical researchers are turning to nonlinear finite element analysis (FEA) to simulate the behavior of these complex lifesaving devices. The patterns developed for stent openings are so complex that the conventional, closed-form equations developed for wire stents cannot accurately predict the behavior. Building and testing physical prototypes is expensive, time consuming, and does not produce

sufficient feedback. Barrel-type cardiac stents are harder to design because of critical tradeoffs between flexibility, expandability, and strength.

Nonlinear FEA software has been used successfully on implantable pacemakers, pacing leads, tip anchoring configurations, heart valves, ablative catheters, angioplasty balloons and stents, drug pumps, blood pumps, oxygenators, orthopedic applications, implantable dental prosthesis, and other devices. Projects often require modeling systems that consist of multiple components with nonlinear materials, complex three-dimensional geometries, and surface-to-surface contacts, as well as coupled conditions that may involve simultaneous mechanical, thermal, electromagnetic loading and fluid-structure interaction. The "MSC.Marc 2000 software," in particular, handles the full range of nonlinear material properties for the stent, the catheter balloon, and the artery wall. The software also has features allowing analysis of the complex 3D contact between these different structures. Simulating the real-world behavior of these types of biomedical systems requires advanced modeling and analysis capabilities, and exceptional preprocessing and postprocessing features for building models and evaluating results. The advanced features of FEA become indispensable tools in the development and certification of stents and other biomedical equipment. Without this computer analysis tool, extensive work in building and testing physical prototypes would be required.

For example, in the development of a new stent, fabricating a device and running through a battery of performance tests requires approximately 90 days, compared to only three to five days for running a computer modeling and simulation program. Prototype testing provides limited data on stent performance, primarily deformed geometry after deployment and regions of failure. The small size of the device makes actual measurements of stress and strain over time impractical (20).

A precise condition where the device must perform over a period of years in a patient's body is difficult to duplicate in a laboratory test. In contrast, FEA is a tool that helps researchers study the as-delivered shape of the stent, what happens when the device is crimped onto the catheter, and how it behaves when expanded in the artery by the balloon. It also shows how the stent performs when subjected to arterial compressive pressure and long-term loading involving millions of cardiac cycles. The FEA results provide mappings of peak stress, plastic strain, and deformations of the stent. These results let researchers evaluate the behavior of a device in the human body, and accurately determine its fatigue life. This information is necessary for complying with FDA submittal requirements, which require a full set of such data before new stent designs are certified. When a problem is detected in the concept configuration, the analyst reports the findings to the designer and they work as a team modifying the stent design and eliminating the problem (20).

B ANALYZING THE LIFE CYCLE

Evaluating the performance of coronary stents entails detailed, individual analysis of three phases in their life cycle:

Packaging and mounting onto the delivery catheter

1. Deployment, as the surgeon guides the catheter-mounted stent to the angioplasty location, then expands it by inflating the catheter balloon.

2. Long-term in-vivo service as the stent is continuously subjected to motion from each heartbeat.

Understanding and accurately simulating the behavior of the structure in each of these phases is essential in predicting overall stent performance. Mounting a stent onto the catheter may subject it to large radial compression forces, deforming and buckling the stent. These large plastic deformations may produce residual stress, which needs to be assessed while the stent is deployed in the vessel. As the cardiologist guides the catheter-mounted stent through the vascular system to the angioplasty site, the stent contacts the vessel walls and bends around "corners." Stents must be flexible when mounted and thoroughly analyzed to prevent damage to the artery or vessel wall. The stent may grow four times its original diameter under catheter balloon pressure. As the balloon inflates, the force makes the stent expand radially outward until it contacts the inner surface of the artery wall. This expansion produces large displacements and plastic strain and stress levels in the stent.

The stents geometry, mounting features, placement, compatibility with the catheter balloon, and the geometry of the vessel opening produced by partial or incomplete angioplasty procedure impact the expansion effects. After simulating the correct method to deliver and deploy the stent, its in-vivo interaction with the artery wall must be evaluated during the cardiac cycle. The stent is usually expanded to a diameter greater than the internal diameter of the artery to ensure that the opening produced by the angioplasty procedure is maintained. When the catheter balloon is deflated and removed, the artery wall attempts to return to its initial diameter and compress the stent. The stent, in its expanded or deployed condition, must be sufficiently stiff and strong to resist compressive buckling failure. The tens of millions of heartbeats experienced by the stent each year make long-term fatigue damage and possible cracking over time a critical concern. Long-term in-vivo loads on the stent result from repetitive cyclical pressure loads and displacement of the artery wall as it expands and contracts slightly with each heartbeat. Also, the cyclical motion of the heart wall where the vessel is attached can bend and torque the stent. This radial deflection typically amounts to less than 10% of the stent's outer diameter (20).

C BUILDING AND EXERCIZING COMPLEX MODELS

Typically, the same finite-element stent model is used in analyzing behavior for all phases of stent mounting, delivery, deployment, and long-term in-vivo service. FEA models must accurately depict the cutout pattern and other design geometry details of the stent. Nonlinear properties of the artery, catheter, balloon, and stent material must be accurately represented. In general, stents in use today are made of stainless steel alloys such as MP35N. But various superelastic or shaped-memory alloys such as Nitinol, and several nonmetallic materials and coatings are being considered for some applications. To provide proper models, the nonlinear characteristics and cyclical loading behavior of these materials must be considered in the stent FEA model. Material stress versus strain test data must be critically correlated with the FEA material models.

For most studies, models consist of eight-node, three-degree-of-freedom (3-DOF) per node, type-7 brick elements. A highly refined mesh is used at the member junctions

to evaluate stress concentration effects upon critical locations. To reduce computation time, partial models are often used to take advantage of geometric symmetry, support, and loading conditions. In many cases, depending on cyclical stent geometry, a segment model may be sufficiently accurate. The stent model simulates the various design conditions to evaluate stent performance. Stent-displaced geometry, stress, and strain are carefully evaluated. The cardiac cycle is simulated in one of several ways: alternating radial displacement of the fully deployed stent, alternating the radial pressure loading applied to the stent, and applying a time-varying cardiac pressure loading to the stent and the contacted elastic arterial wall (20).

D HOW DOES FEA FECILITATES DESIGN?

After the designer develops an initial configuration, it is turned over to analysts for modeling and analysis. The FEA model data includes stress and strain distributions, deflected geometry, and fatigue loading effects for each phase of the analysis work. Computer simulation is a particularly valuable tool in revealing potential problems with deflected geometry or stress levels. In some cases, the catheter balloon material may bulge through the slots of the stent and hamper proper expansion. The ends of the stent may expand much faster than the body, flaring the ends of the device, which could damage the artery wall. Correlating the results of numerical simulations with real-world test data is crucial in verifying the accuracy of FEA model results, as is developing accurate correlation of material test data with the FEA materials.

Prototype stents may be compressed, inflated, and bent in the laboratory, and their test data correlated with FEA model simulations to verify the accuracy of the model results. In evaluating the long-term in-vivo service of a particular stent, designers ensure the device has the strength to balance the radial compression of the stent when the artery is being subjected to cyclic cardiac pressure loading. The design objective is a uniform expansion of the stent, while maintaining maximum stress levels at or below the allowable design limits, and preventing geometric instability. Researchers closely watch for large deformations, crimping, buckling, or other problems in the stent that may exceed the design stress limits, causing a possible collapse, fracture, or fatigue failure. When a problem is detected in the concept configuration, the analyst reports the findings to the designer and they work as a team modifying the stent design and eliminating the problem. The new design is analyzed again until an optimum design emerges from their efforts. In this way, analysis guides the design to meet the required specifications for a reliable product (20).

5.6 REGULATORY STANDARDS FOR STENTS

A HOW TO GET DEVICES TO THE MARKET (17)?

The Food and Drug Administration (FDA) has three steps that should be followed to have a medical device accepted in the market. But to be able to follow these steps, the manufacturer needs to pass through the general controls of the Federal Food Drug and Cosmetic Act (FD & C Act), which are contained in the final procedural regulations in Title 21 Code of the Federal Regulations Part 800–1200. General controls are basic authorities to the Food, Drug and Cosmetic Act that provide the FDA with means of regulating devices to ensure their effectiveness and safety. The first thing is to know

what one is trying to get to the market qualifies to the FDA as a medical device. These controls are the requirements that apply to all medical devices.

After one has completed these regulations and controls, the person wants to enter the market to meet the definition of what a medical device is as proposed by the FDA. A medical device ranges from simple tongue depressors and bedpans to complex programmable pacemakers with microchip technology and laser surgical devices. Medical devices also include in vitro diagnostic products, such as general-purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology. There are also some electronic radiation emitting products with medical application and claims meet the definition of medical device to the FDA. Second Step is to classify the device. There are three classes in the FDA. For example, class I are not intended to be: for use in supporting or sustaining life; of importance in preventing impairment to human life; and may not present a potential unreasonable risk of illness or injury. As you can see this classes Identify the level of regulatory controls necessary to assure the safety and effectiveness of the medical device as well as the premarket approval to have clearance of approval for marketing (17).

The third step is the development of data and information necessary to submit marketing application and to finally obtain FDA clearance to market. Clinical performance data is required to obtain clearance to market and has to be done according to FDA's Investigational Device Exemtion (IDE) regulation (17).

B TITANIUM FOR MEDICAL DEVICES

Titanium has high strength, low weight and outstanding corrosion resistance. They have a diversified range of successful applications which in the performance of medicine and surgery are in high demand. Because of it great properties it is not only used in medicine but also used in aerospace, chemical plants, power generation and other major industries. Titanium is one of the few materials that naturally match the requirements for implantation in the human body because it is light, strong and biocompatible (8).

Titanium alloys have a significantly higher strength to weight ratio than challenging stainless steels. Because of the range of availability of titanium alloys medical specialist designers can select the material that can feel the need of the application being made. Titanium alloys ranges from high ductility to heat treatable alloys with strength above 1300 MPa (190 ksi) (8). One thing that is very important is that what we install in the body cannot be readily maintained or replaced. Because of this the reliability and effectiveness of implants, medical and surgical instruments and devices is a very important factor in saving lives and relieving long-term relief from pain and suffering. Because of its importance, we have to verify that the titanium corrosive resistance of the titanium.

Titanium is known to be immobile and immune to corrosion by body fluids and tissues, in other words it is bio-compatible. The good biocompatibility and corrosion resistance of titanium are due to the stable titanium oxide (TiO_2) film that naturally forms on titanium surface. When designing and building the stent we have to choose the right titanium. This includes that the titanium has immunity to corrosion, strength, low modulus and density bio-compability, and Osseo integration-capacity of joining

with other tissues and bones. The human anatomy naturally limits the shape and allowable volume of implants. The lower modulus of titanium alloys compared to steel is a positive factor in reducing bone absorption. But the two parameters that define the effectiveness of the implantable alloy: the notch sensitivity-ratio of tensile strength in the notched and un-notched condition- the resistance to crack propagation or fracture toughness. Titanium possesses both parameters. Typical NS/TS ratios for titanium and its alloys are 1.4–1.7 (1.1 is a minimum for an acceptable implant material). Fracture toughness of all high strength implantable alloys is above 50 MPam-1/2 with critical crack lengths well above the minimum for detection by standard methods of nondestructive testing (28).

Titanium is used for cardiovascular devices. It is regularly used for defibrillators and pacemaker cases as carriers for structures for the substitution of heart valves and intravascular stents. Another good thing is that titanium can withstand repeat sterilization without compromise to edge or surface quality, corrosion resistance or strength. Titanium is non magnetic, and there is therefore no threat of damage to small and sensitive implanted electronic devices (28).

C NITINOL BIOCOMPATIBILITY (19)

Nitinol was the first practical biomaterial accessible to the medical community. The stiffness and shape of Nitinol is controlled with temperature making it possible to prepare functional implants activated at body temperatures. Nitinol also has superelasticiy and can be used in implants open to the elements of distorsion or kinking. Because of these properties, Nitinol is an appealing implant material.

Nitinol shows a shape memory effect. This means that when it is deformed at low temperatures and subsequently heated, it reverts to its original shape. During this process, the metal undergoes a complex crystalline-to-solid phase change called martensite-austenite transformation.

The biocompatibility studies of Nitinols have indicated that nickel can be of harm to the human body because of toxic effects, local tissue irritation and carcinogenicity. Because Nitinol contains high contents of nickel, it is possible based on theory that nickel may liquefy from the material due to corrosion and cause adverse effects. Due to this, biocompatibility studies of Nitinol in different tissues of the body are very important before clinical use in these tissues.

Nitinol is used in a variety of stents on arteries, esophagus, biliary obstruction, colon, urethra, major airway obstruction and lacrimal system obstruction. Simon Nitinol Filter was one of the earliest functional Nitinol Implants that was used to prevent pulmonary embolism. Nitinol is also used in the carotid stents to help with the blockage of blood flow through the carotid artery caused by plaque. Then in the year 1993, a self-expanding prosthesis of Mersilene, strengthened with a cross- or star-shaped Nitinol wire, was introduced into laparoscopic hernioplasty. Another promizing application is a NiTi hook used to restore the dislocated acromio-clavicular joint (19).

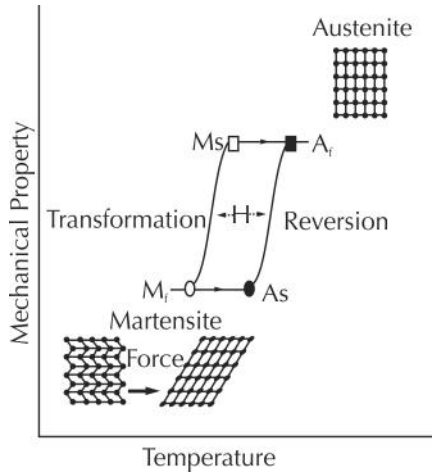

FIGURE 6 Martensite – austenite transformation (28).

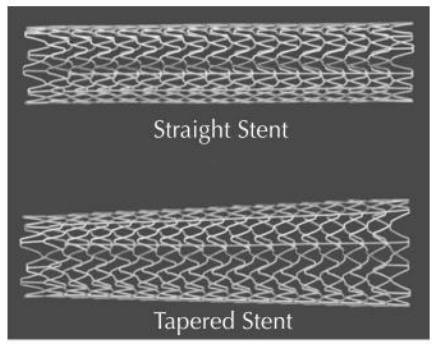

FIGURE 7 Stainless Steel 316L Stent (18).

5.7 BIOMATERIALS FOR INTRACORONARY STENTS

Intracoronary stents are frequently made of stainless steel, tantalum and nitinol. Of these, stainless steel is the most common. It is durable and has a relatively high radiopacity, a property of the material that prevents the passage of *x*-rays or any other radiation. Tantalum has a better radiopacity than steel. Nitinol is a nickel-titanium alloy with unique self-expanding properties. This property allows the stent to expand into the walls of the blood vessel and acquire a better grip. The stent also offers the possibility to circumvent emergency bypass surgery in case of PTCA related vessel occlusion (26).

1 TANTALUM STENTS

Tantalum is a shiny, flexible, and highly radio-opaque metal. Though more brittle than stainless steel, tantalum exhibits high ductility and resistance to corrosion. Current examples of tantalum stents include the Wiktor Stent by Medtronic and theTantalum

Cordis Stent. However, newer models like the drug-eluting stents have yielded lower restenosis and revascularization rates. Tantalum is ideal for viewing and supporting, but more biocompatible options exist. Table 1 shows the properties of Tantalum (26).

1. Significantly affected by increasing interstitial contents.
2. Tantalum stent can be placed with a high rate of success.
3. It may also reduce the risk of restenosis.

2 STAINLESS STEEL 316L STENTS

Most stents are crafted from 316L stainless steel. Current examples include the Cordis Palmaz-Schatz stent, the Cordis Crossflex stent, the Guidant MultiLink stent, and the Medtronic Bestent. Disadvantages of steel stents include the high occurrence of subacute thrombosis and restenosis, bleeding complications, corrosion, and redilation of the stented vessel segment.

According to the Medtronic website, the "adverse effects" of stents are "death, myocardial infarction, CABG, stent thrombosis, bleeding complications, stroke, vascular complications, stent failures; potential adverse events, e.g., acute myocardial infarction, myocardial ischemia, arrhythmias, dissection, distal emboli, hemorrhage, perforation, restenosis of stented segment, stent embolization and total occlusion of coronary artery." The radiopacity, or viewing capacity of stainless steel stents could also be improved (25).

1. Stainless steel is a common inexpensive and relatively biocompatible stenting material in use today.
2. 316L – reduced carbon content from 0.08 wt% to 0.03 wt% to further improve corrosion resistance in chloride solutions.
3. 316 – addition of molybdenum to improve corrosion resistance in salt water.
4. Austentitic category – contain FCC iron.
5. Not hardenable by heat treatment, but can be hardened by cold working.
6. Non-magnetic.
7. Contain Iron, chromium, nickel, molybdenum, manganese, silicon, carbon, phosphorous, and sulfur. Last four elements are trace elements, with a maximum concentration of 0.75 wt% each. Young's modulus is about 210 GPa.
8. 302 stainless – stronger and more corrosion resistant.
9. Oxidizes to form transparent film on surface of material, sealing surface and preventing other oxidants from reaching the metal.
10. Stainless steel would stay crushed, holding the artery closed).

3 NITINOL STENTS

Nitinol (from the "Nickel Titanium Naval Ordinance Laboratory") is an example of a biocompatible, super-elastic shape-memory alloy. As a shape-memory alloy consisting of 55% nickel and 45% titanium, nitinol has the ability to return to a specific shape upon heating to a certain temperature after its phase transition. Shape-memory alloys undergo a phase transition in their crystal structure when cooled from their stronger, higher temperature form in the Austenitic phase to their weaker, lower temperature form in the Martensitic phase. Nitinol also has a springy, "rubber-like" behavior that allows it to be super-elastic and contorted at its austenitic temperature (Fig. 6).

The strong intermetallic bond between nickel and titanium has a very low reaction rate, even in patients with increased sensitivity to nickel. This prevents a strong immunological response and decreases corrosion. Alan Pelton, research fellow at Nitinol Devices and Components, a subsidiary of Johnson & Johnson in Fremont, CA, says: "…having shape memory properties and being biocompatible, nickel-titanium probably has the market tied up for quite a while." However, nitinol is also difficult to manufacture. A mere tenth of one percent change in its composition can drastically alter the transformation temperature. Also, the titanium component in the alloy is highly reactive with oxygen and nitrogen particles in the air, so all alloy formation must occur in a vacuum. Only about 5% of stents today are made of nitinol. Present examples include Boston Scientific's Nitinol-self expanding Radius stent. Boston Scientific's Symbiot stent, available in Europe, is comprised of nitinol covered on both sides by 16-micron thick layers of ePTFE (23).

4 CO–CR ALLOYS STENTS

The introduction of Co–Cr alloys in a new generation of stent has enabled a reduction in strut thickness, which has been shown as a positive factor for clinical performance. Selected material properties influencing stent performance have been reviewed for L605, Phynox/Elgiloy and MP35N. With a higher density and elastic modulus, L605 appears of particular interest. Experimental results are showing the range of properties achievable on stent size tubing.

Their dependence on cold work and final anneal temperature is described for a cold work range of 0 to 45% and a temperature window of 900 to 1175°C. This allows stent designers to select the optimal material properties for the device. The wide range of material properties requires control of the cold work and annealing during tube and stent manufacturing (22).

The advances in the field of biomaterials help to minimize the cost of the operations and products without decreasing the quality of the product. In the future, more efficient materials can be found to lower the cost of treatment for Carotid Artery Stenting and other Procedures.

TABLE 1 Properties of Tantalum (8).

Property		Units	Value
Ultimate tensile Stength	Annealed		
		MPa	285
		Ksi	41
Yield Strength		MPa	170
		Ksi	25
% Elongation		%	30
% Reduction In area		%	80

TABLE 1 *(Continued)*

Property		Units	Value
Ultimate tensile Stength	Cold worked	MPa	650
		Ksi	95
% Elongation		%	5
Hardness	Annealed	HV	90
	Cold worked	HV	210
Poisson's ratio	——	—	0.35
Strain hardening exponent	——	—	0.24
Elastic modulus	Tension	GPa	186
		Ksi	27000
	Shear	——	——

TABLE 2 Properties of 316 grade stainless Steels (2).

Property	Units	316	316L	316H
Tensile Strength *	MPa	515	485	515
Yield Strength *	MPa	205	170	205
Elongation (in 50 mm) *	%	40	40	40
Hardness Rockwell	Max	95	95	95
Hardness Brinell	Max	217	217	217

* Minimun value.

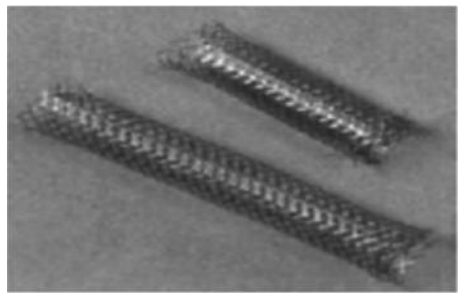

FIGURE 8 Nitinol Stents (16).

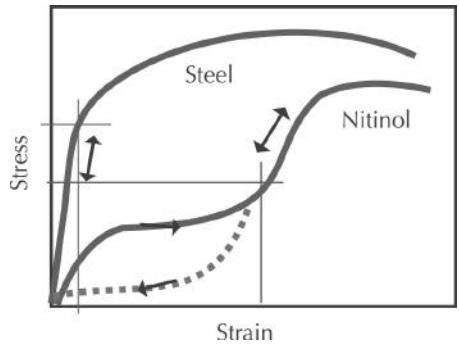

FIGURE 9 Stress-strain curve for nitinol and steel (28).

5.8 SUMMARY

Carotid Arteries bring oxygenated blood from the heart to each side of the head. Blockage of Carotid Arteries can create a lack of oxygen caused by insufficient blood flow, which can ultimately cause an ischemic stroke. Carotid Stenting is a procedure in which a tiny, slender metal-mesh tube is fitted in the artery to increase flow of blood blocked by plaques during agioplasty. After this a balloon-tipped catheter is inserted into the blocked artery to flatten the plaque and reopen the artery through. In this chapter, four biomaterials are presented for the design and manufacture of stents and balloon-tipped catheter. These are: Tantalum, NiTinol (Nickel-Titanium), and 316 L Stainless Steel. The materials are selected based on yield stress, strain, resistance, modulus of elasticity, and biocompatibility, etc.

In this chapter, we have learned about different types of biomaterials for carotid stenting. They must be biocompatible and approved by FDA to be able to be placed in the body. In conclusion, definitive treatment of extracranial carotid disease is well entrenched for patients with both symptomatic and asymptomatic severely stenotic lesions. The gold standard remains open surgical endarterectomy, but there is intense interest in carotid stenting from the clinical and investigative perspective. Initial results of stenting appear to be quite reasonable, challenging traditional endarterectomy in low-risk patients and probably surpassing endarterectomy in higher-risk subgroups. With advances in stents, delivery systems, antiembolic devices and, most important, the technical expertise of the operators, it is likely that carotid stenting will become the treatment of choice for patients with significant carotid disease.

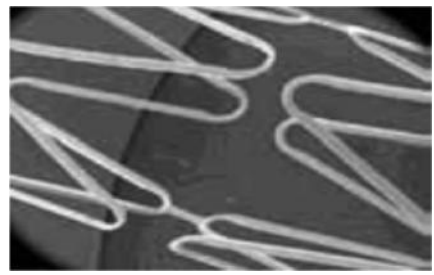

FIGURE 10 Nitinol (23).

TABLE 4 Properties of Co-Cr alloys (23).

Property	Units	L605	MP35N	Phynox
Elastic Modulus	GPa	243	233	221
Ultimate Tensile Strength *	MPa	1000	930	950
Yield Strength *	MPa	500	414	450
Tensile Elongation *	%	50	45	45

*Minimun value

TABLE 5 Properties of Biomaterials (2, 8, 23, 28)

Property	Units	Niti*		Tantalum	SS 316L	Co-Cr MP35N
		High	Low			
Poisson's Ratio	—	0.3	0.3	0.35	0.29	0.32
Hardness	Vickers	62	—	100	199	50
Young's Modulus	GPa	75	28	186	193	233
Shear Modulus	GPa	29	11	69	78	83.4
Yield Tensile Strength	MPa	560	100	170	330	414
Ultimate Tensile Strength	MPa	754–960	754–960	450	585	930
Elongation at Break	%	15.5	16	30	45	45
Heat Capacity	J/g-C	0.32	0.3	0.153	0.5	.42
Thermal Conductivity	W/m-K	10	10	54.4	18.5	11.2
Thermal expansion Coefficient	10^{-6}/F	—	—	—	10.4	—
Maximum	10^{-6}/C	11	—	6.5	18.8	12.8

KEYWORDS

- **Alloy**
- **Angioplasty**
- **Ballon-tipped Catheter**
- **Balloon catheter**
- **Balloon expandable stent**
- **Endovascular stent**
- **Graft vasculature**
- **Inflatable balloon**
- **Intravascular stent**
- **NiTinol**
- **Self-expanding Stent**
- **Stainless steel**
- **Stent**
- **Stent delivery system**
- **Vascular stent**

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CHAPTER 6

BIOMECHANICS OF ANGIOPLASTY: BALLOONING AND STENTING[1,2]

CONTENTS

[1] This chapter has been modified from the review article prepared by my students (Luis A. Alicea, José J. Torres Alvarado and Alexis Vargas Martínez) for the course on Fluid Mechanics, INGE 4015. Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com≥ or visit at: http://www.ece.uprm.edu/~m_goyal/home.htm. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2] The numbers in parentheses refer to cited references in the bibliography.

6.1 INTRODUCTION

Stents are generally used instead of – or along with – angioplasty. It is collapsed into a small diameter and put over a balloon catheter. It is moved into the area of the blockage. When the balloon is inflated, the stent expands, locks in place and forms a scaffold. Stents need to be resistant and elastic to fulfill the procedure. Vascular stents keep diseased arteries open to a predetermined diameter after angioplasty and preserve a cylindrical lumen. Currently, there are two categories of stents: balloon expandable and self expandable (Fig. 1). Balloon expandable stents are typically cut from small diameter stainless steel tubing, mounted over an angioplasty balloon and then plastically deformed to final diameter. Self-expandable stents are stainless steel, tantalum, or nitinol and are usually compressed into a small diameter delivery catheter where they can be delivered to the deployment site. These stents are either cut from tubing or fabricated as a wire mesh (30).

Although most existing stents perform the function of supporting diseased arterial tissue, stent design profoundly influences the reaction of the artery wall. Studies have revealed that stent structure influences thrombus accumulation between struts and restenosis. Coronary restenosis is dependent on vessel size and stent design. Moreover, the pattern of accumulation appears similar to the zones of flow stagnation predicted upstream and downstream of stent struts using Computational Fluid Dynamics (CFD). Rogers and Edelman (Cited from 30:499) reported significantly less neointimal hyperplasia in balloon expandable stent designs fabricated with reduced strut–strut intersections. They concluded that stent struts disrupt the arterial wall greater than balloon angioplasty alone. Fewer struts minimized strain in the tissue and also possibly caused less denudation of endothelial cells. Unfortunately, none of these studies included careful analysis of the mechanical environments in the different stent designs being tested.

The evidence implicating specific flow patterns in atherosclerosis and vascular graft failure provides convincing motivation for further stent related investigations. CFD studies in the human aorta, carotid arteries, and coronary arteries have shown a strong correlation between intimal thickening and specific flow patterns occurring at focal locations in these vessels. Low mean shear stress, oscillating shear stress, high particle residence times, and nonlaminar flow are known to occur in the locations where early intimal thickening is greatest. Studies in both end-to-side and end-to-end anastomotic geometries have indicated that similar flow patterns are found in the specific areas where vascular grafts are known to develop stenosis. In addition, compliance mismatch between vascular graft and host vessel is implicated as a culprit in neointimal hyperplasia (30). This chapter includes information on: Angioplasty, atherectomy, fluid dynamics, computational fluid dynamics, ballooning and stents.

6.2 ANGIOPLASTY

Percutaneous transluminal coronary angioplasty (PTCA) or angioplasty is an invasive procedure performed to reduce or eliminate blockages in coronary arteries. The goals of PTCA are: To restore blood flow to blood-deprived heart tissue, reduce the need for medication, and eliminate or reduce the number of episodes of angina (chest pain).

Opening a blockage or a plaque, in a coronary artery typically involves the use of an angioplasty balloon. When the blockage is calcified or so dense that a balloon cannot be placed, alternate procedures are used, such as: Plaque can be cut out, vaporized with a laser, or bored out using a surgical drill bit. Often, a stent is implanted after angioplasty to keep the artery open and prevent restenosis (regrowth of plaque).

The arteries are accessed through a needle puncture made in the groin (femoral artery) or arm (brachial artery). Usually the femoral artery is used. More than one blockage can be treated during a single session, depending on the location of the blockages and the condition of the patient.

INDICATIONS

Angioplasty is recommended for patients with one or more of the following symptoms:

- Blockage (stenosis) of one or more coronary arteries.
- Angina not well controlled with medication.
- Angina that disrupts daily activities, occurs at rest (i.e., without exercise or exertion), or recurs after heart attack.

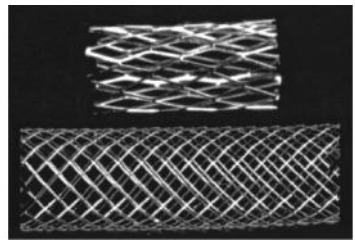

FIGURE 1 A balloon expandable stent (30).

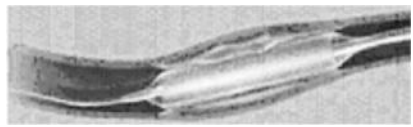

FIGURE 2 Balloon Angioplasty (23).

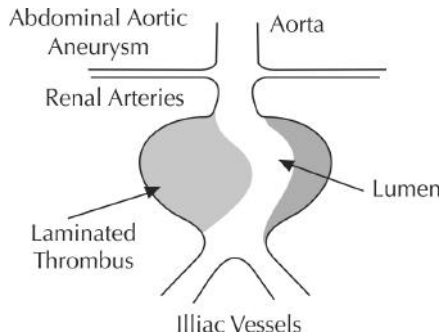

FIGURE 3 A schematic depiction of an abdominal aortic aneurysm (21).

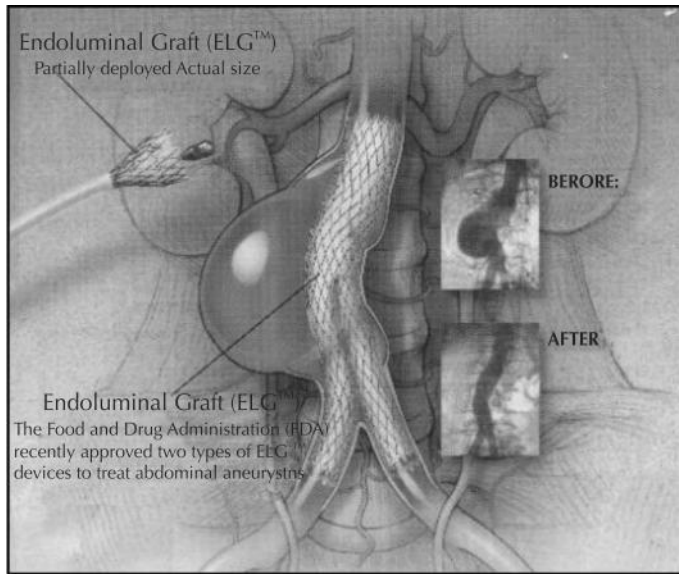

FIGURE 4 Ballooning (30).

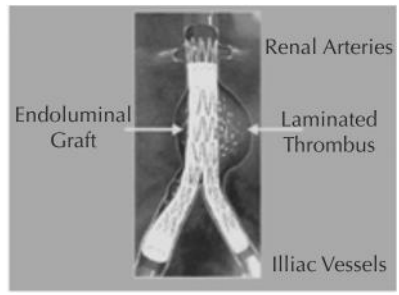

FIGURE 5 The AAA graft system (21).

6.2.1 PREPROCEDURE

An IV is started to administer medication to prevent blood clot formation during and after the procedure. Heparin, an anticoagulant, is given alone or if the patient has unstable angina or other high-risk factors, with GP IIB/IIIA receptor inhibitors (e.g., abciximab, tirofiban). These agents lower the risk and complications due to blood clot formation.

Angioplasty is performed in a catheterization laboratory equipped with X-ray equipment and monitors. In the catheterization laboratory, the insertion area is cleansed with a sterilizing solution, covered with sterile drapes, and numbed with a local anesthetic. An incision is made and a pencil-sized plastic sheath is inserted. Flexible catheter is passed through the sheath to the blocked coronary artery. The device to open the artery (e.g., balloon, laser, burr) is advanced to the blockage through the catheter. An iodine-based dye or other contrast agent is injected to make the arteries

and blockage(s) visible on a monitor. Physicians use a monitor to guide the catheter during the procedure.

6.2.2 BALLOON ANGIOPLASTY

Balloon angioplasty is performed alone or after atherectomy. In this procedure, a guide wire (Fig. 2) is threaded through the blockage, and a thin, un-inflated balloon is passed to the tip of the wire. Once properly positioned in the artery, the balloon is inflated for approximately two minutes to press open the blockage and create a channel that increases blood flow through the artery. Chest pain may be experienced during the procedure if the artery is completely blocked while the balloon is inflated. A larger balloon is used to enlarge the opening. Once a channel has been created, a stent may be implanted to maintain the opening (23).

Abdominal aortic aneurysm (AAA) is a ballooning of the abdominal aorta. If this aortic 'balloon' ruptures, the consequences for the patient can be catastrophic. This disease is more common among elderly persons and is a possible consequence of insufficient exposure to ultraviolet light during the developmental stages of childhood and adolescence (21).

Fig. 3 indicates the anatomical structure and the 'laminated thrombus.' The path of the blood through the laminated thrombus is known as the 'lumen' (51). If left untreated, an AAA will continue to expand until it bursts. The bursting of a major artery such as the aorta can lead to severe internal bleeding and can be fatal. In the past, open repair was the only treatment option available. Unfortunately, such an operation is a traumatic and stressful experience, particularly for an elderly patient. Indeed, about 5% of open-repair patients die due to the operation itself. In an effort to reduce these negative aspects, an alternative procedure was developed where a pipe or 'graft' is introduced, typically via the illiac vessels, into the AAA. If placed correctly, blood will flow through the graft and relieve the stress on the AAA walls. It then takes about two years for the aneurysm to heal, after which time the patient is effectively cured. A schematic of a ballooning is shown in Fig. 4. A depiction of the graft AAA system is given in Fig. 5.

6.3 ATHERECTOMY

Atherectomy is a procedure to remove the arterial plaque. There are four types of atherectomy: laser, rotational, directional, and transluminal extraction. Laser atherectomy (Fig. 6) is commonly used to remove enough plaque to allow balloon angioplasty to be performed. In this procedure, a laser attached to the tip of a thin flexible catheter emits short pulses of light that vaporize plaque. Rotational (or rotablator) atherectomy is used to treat artery with very long, calcified, or solid blockages. This technique also can be employed to remove plaque that has regrown inside a stent. In this procedure, a burr, or surgical drill bit, tipped with very fine diamond chip (Figure 7) is carefully advanced to the blockage. Compressed air spins the burr to pulverize the plaque and the debris is continually suctioned out. Progressively larger burrs may be used to enlarge the channel in the artery.

After rotational atherectomy, the channel is usually expanded further with an angioplasty balloon, and in many cases a stent is permanently implanted to hold the

artery open. Directional atherectomy employs a catheter tipped with a device consisting of a cup-shaped blade and a container. The blade cuts away plaque from the artery and deposists it into the container.

Transluminal extraction involves a special catheter tipped with a hollow tube and rotating blades. As the blades cut plaque away from the arterial wall, the debris is suctioned out of the body through the tube (30).

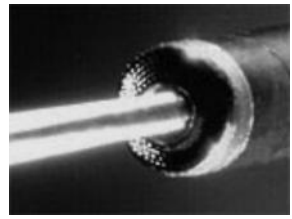

FIGURE 6 Laser atherectomy beam (23).

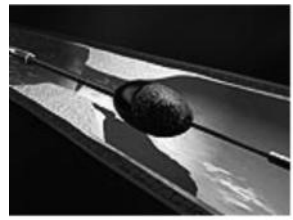

FIGURE 7 Rotation atherectomy (23).

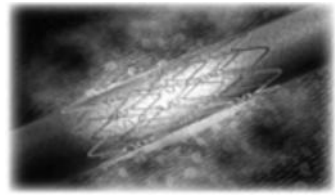

FIGURE 8 Drug eluting stent (32).

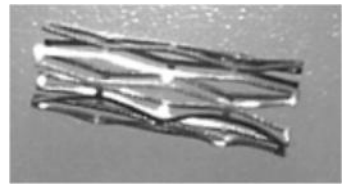

FIGURE 9 Radioactive Stent (32).

6.4 RESEARCH ADVANCES

6.4.1 DRUG-ELUTING STENT

A stent is a spring-like device that is temperature sensitive. Compressed and supercooled, it is inserted into an artery, routed through the body and deployed at the point of an aneurysm, at which time it expands to its desired diameter and supports the walls of the artery. It is necessary to ensure that the stents expand at the proper rate and to the proper size. A mistake can be life threatening (32). Many types of technologies have been researched over the years to help solve the problem of restenosis. Currently there is increasing interest in a technology that brings together a drug and a stent. The drug is placed on the stent with a process that allows the drug to be released over time. This is called a drug-eluting stent (Fig. 8). A drug-eluting stent is coated with a drug that is designed to control the release of a drug into surrounding tissue. The intention of this time-release process is to slow down the growth of unwanted cells (restenosis) and allow the vessel to heal.

Due to the build up of scar tissue within the stented segment, approximately 15–30 percent of stented arteries reblock (restenosis) within the first year. These patients must be treated again with a procedure such as repeat angioplasty or bypass surgery. Drug-eluting stents have been shown to reduce the restenosis rate by 80 percent (32). "Development of stents was a significant milestone in the treatment of blocked coronary arteries, but the problem of restenosis has continued to be an issue, " indicates Stephen H. Hindman, M.D. "Sirolimus-coated stents will deter the scar tissue from forming. We have been waiting for a new technology to improve the quality of life of a patient suffering from clogged artery. This is an important advancement for cardiologists in the treatment of coronary artery blockages. Patients who receive these devices will need fewer repeat operations, " indicates Judy Henderson, RN, director of Baptist Cardiovascular Diagnostics (4).

6.4.2 RADIOACTIVE STENT

Radioactive stent can inhibit recurrent blockage of arteries (restenosis) following angioplasty. Here, we shall explore alternative methods to produce a calibration technique for the stents related to national standards. Air kerma strength is calculated after charge is collected in an ionization chamber at consecutive distances from a stationary source, known as the "seven distance technique." This technique has been extended to a Low Dose Rate (LDR −192Ir) source in preparation to measure the 198Au stents. The emitted gamma ray energies are similar for these two isotopes: 198Au E (gamma) = 405 keV and 192Ir E (gamma) = 397 keV. This is an effective calibration tool for 198Au radioactive stents.

6.4.2.1 RADIOACTIVE STENTS FOR THE PREVENTION OF RESTENOSIS

The stents use P-32 with a half-life much longer than the acute cellular proliferation phase, and too short to provide long-term inhibition. Researchers have been experimenting with radionuclides: reactor-produced Au-198. The first requirement is consistency with the calibration procedure that applies to all radionuclides. The basis for this calibration is a concentric cylindrical extrapolation chamber. The second requirement is a methodology for calculating the dose distribution delivered from a deployed stent

to the surrounding tissues. This calculation will use intravascular ultrasound to determine the actual geometry, and sum the contributions of the parts of the stent in each image. Monte Carlo simulations will determine the contribution from small parts of the stent. This technique also addresses tailoring the source distribution along the stent to produce the optimal dose distribution.

6.4.2.2 FABRICATION OF RADIOACTIVE STENTS BY ION IMPLANTATION

A tubular stainless steel mesh (stent) is implanted to mechanically support the injured vessel. Restenosis, an abundant complication (20–30%) can be prevented, if the vessel is treated with ionizing radiation. The radioactive stent can deliver radiation. The radio isotope ^{32}P is well suited when ion implanted. Radioactive ions source requires high efficiency to keep the radioactive inventory small. Reliability, ease of operation, and maintenance are mandatory. A small emittance is important to minimize losses during mass separation and beam transport. A 2.45 GHz ECR source was developed for the implantation of ^{32}P. The source consists of two coils for the axial and a permanent hexapole for the radial confinement. The microwaves are fed in radially by a loop connected to a silver plated brass tube surrounding the plasma chamber. The plasma chamber is made from pyrex. Neutron activated phosphorus, containing 30 ppm of ^{32}P, is introduced from the rear end on a rod. As support gas D_2 is used. By this $^{32}P^+$ can be separated from $(^{31}PD)^+$. The extraction is done in two steps: 60 kV–30 kV ground. Mass separation is accomplished by a double focusing 90° magnet (radius 500 mm). During four years of operation, about 1000 radioactive stents per year have been provided for animal experiments and clinical trials. It takes onlyone maintenance to exchange the extraction system due to degradation of high voltage stability.

6.5 INDICES OF CORONARY FLUID DYNAMICS (9)

The internal Left Anterior Descending (LAD) coronary radius (r_i) is determined by the following equation:

$$r_i = \left(r_0^2 V / L\pi\right)^{1/2} \tag{1a}$$

Where: r_0^2 is the external LAD radius, L is the length between proximal and distal Doppler flow velocity probes in situ, and V is the ratio of the excised vessel weight to blood density (= 1.06 g/mL). Reynolds number (Re) describes the ratio of convective inertial forces to shear forces in a cylinder and is calculated by Eq. (1):

$$\mathrm{Re} = (2r_i)\cdot \rho \cdot (/\mu) \tag{1}$$

Where: ρ is the blood density (1.06 g/mL) and $\bar{\nu}$ is the temporal mean flow velocity of the blood flow and μ is blood viscosity. Dean number (De) is related to the secondary flow and considers the effects of coronary artery curvature on the axial velocity profile. The De is determined using Eq. (2):

$$\mathrm{De} = ((2\delta)^{1/2})\cdot (4\ \mathrm{Re}) \tag{2}$$

Where: δ is the ratio of LAD r_i to the radius of curvature. The Womersley number (α) characterizes the ratio of oscillatory inertial forces to shear forces and is estimated as the product of LAD r_i and the square root of the ratio of angular frequency to μ. Secondary Reynolds number (Re_s) considers the combined actions of LAD pulsatility and curvature and is approximated as (De (4))[2]. Regional shear rate (γ) is estimated from coronary blood flow rate ($\omega\dot{Q}$) and r_i with Eq. (3):

$$\gamma = 4\dot{Q}/\pi r_i^3 \tag{3}$$

and refers to the temporally varying shear rate on the walls of the epicardial LAD.

Mean and diastolic coronary vascular resistances are calculated as the ratios of mean and diastolic arterial pressures to mean and diastolic coronary blood flows, respectively. Coronary flow reserve is estimated as the ratio of maximum blood flow during vasodilation to resting flow. LAD segmental compliance © in the region designated for stent implantation is determined with the following equation:

$$C = (\pi(dD) \cdot d \cdot L)/(2dP) \tag{4}$$

Where: d*D* is a change in the diameter 0f the LAD, *d* is a maximum internal diameter of the LAD, dP is the change in arterial pressure during diastole, and *L* is the length of the deployed stent. Additionally, Poiseuillean resistance (PR) in the stented region is defined as: PR = 8 μ*Lπr*.

6.5.1 COMPUTATIONAL FLUID DYNAMICS (CFD): FORCES ON GRAFTS/STENTS (21)

The derivation of the mathematical structure of the equations for the flow of Newtonian fluids (such as water) allows nondimensional numbers to characterize the flow. For an artery, the Reynolds number (Re) is defined as:

$$\mathrm{Re} = \frac{\rho \cdot u \cdot D}{\mu}, \tag{5}$$

Where: *D* is the artery diameter, ρ is the mass density of the blood, *u is* the speed of the blood flow and μ is the dynamic viscosity of the blood. The typical Reynolds number range of blood flow varies from one in small arterioles to approximately 6,000 in the aorta, the largest artery. To simulate the blood flow through the graft, we must have knowledge of the rheology of blood. From the experimental data available in the literature, blood can be described mathematically as a Casson fluid, i.e., as a Newtonian fluid with a yield stress. Due to the relatively large size of the aorta and speed of blood flow through an abdominal aortic aneurysm (AAA), it can be assumed that blood behaves as a Newtonian fluid. Physically, this means that the shear stress, τ, in the fluid and at the wall of the graft is proportional to the velocity gradient in the fluid and the fluid viscosity. Newton's Law of viscosity is defined as:

$$\tau = \mu \cdot \frac{du}{dy} \tag{6}$$

Where: μ is the dynamic viscosity of the fluid, *u* is the fluid speed and *y* is the distance from the wall of the graft. The rheological properties of blood are assumed to be constant with $\mu = 0.0036$ N/m^2 and blood density $\rho = 1.060$ kg/m^3. To simulate the velocity and pressure of the blood in the graft, we need to solve the Navier- Stokes equations for fluid flow. These equations are basically Newton's Second Law for fluids. For a particle, Newton's Second Law of Motion has the form shown in Eq. (7):

$$a = \frac{R}{m} \tag{7}$$

Where: *a* is the acceleration of a particle with mass, *m*, subject to a resultant force, *R*. For a Newtonian fluid, the Navier-Stokes equations in the vector notation is:

$$\frac{dv}{dt} + v \cdot \nabla v = -\frac{1}{\rho} \cdot \nabla p + v \cdot \nabla^2 v, \quad in \quad \Omega, \tag{8}$$

Where: *v* is the velocity, *p* is the pressure, *v* (= μ/ρ) is the kinematic viscosity and Ω is the integration domain of interest. The term on the left of this equation is the acceleration of the flow, while the term on the right consists of the pressure force and the frictional force due to viscosity. In principle, the three Navier-Stokes equations allow us to compute the three components of the flow velocity, provided that we know the pressure field. Often, the pressure field is unknown; therefore the continuity or mass conservation equation is used to provide the required fourth equation to solve the system. The continuity equation for an incompressible fluid is given below:

$$\nabla \cdot v = 0, \quad in \quad \Omega \tag{9}$$

The Eq. (9) implies that total flow into the system must be equal to the total flow out of the system. It is assumed that the blood flow is steady (i.e., nonpulsatile) and turbulent. The steady state assumption is made for computational convenience and should give a moderately accurate value for the peak forces on the graft if peak flow rates are used. Initial CFD simulations were undertaken on a graft with the dimensions shown in Fig. 10. For initial calculations, it is assumed that the distal legs of graft are of same length and diameter. In reality, most grafts have legs of different lengths and diameters. Nonetheless, it is important to understand this symmetric case first. The finite volume mesh of the computational domain is shown in Fig. 11. The total number of computational nodes is 53,065. For this symmetric geometry, it is assumed that the flow is equally split between the two legs. Given this assumption, the equations of mass conservation can be used to show that the expected exit speed of the blood from the graft should be:

$$v_{exit} = \frac{1}{2}\left(\frac{D_{inlet}}{D_{exit}}\right)^2 v_{inlet} \approx 2.7 m/s \tag{10}$$

Where: v_{inlet} = 0.6 m/s, D_{inlet} = graft inlet diameter = 3 cm and D_{exit} = 1 cm. This exit speed is in agreement with CFD simulations that give an average outlet flow speed of 2.77 m/s. The CFD flow results for the symmetric endoluminal graft are listed in Table 1. The inlet pressure *p*inlet was 13.3 kPa. This value was assumed because a mean pressure of approximately 100 mmHg is often observed in the aorta. The velocity results for the entire graft are shown in Figs. 12 and 13. As expected, the speed of the flow increases as the blood travels from the proximal to the distal ends of the graft. This is due to the decreasing diameter of the pipes.

6.6 SIMULATIONS OF ARTERIAL FLOW DISTURBANCE INDUCED BY INTRAVASCULAR STENTS (11)

6.6.1 STRAIGHT VESSEL SIMULATIONS (11)

Figure 14 demonstrates the effect of the number of rings on the length of the separated flow zone downstream of the stent (L) for three different Reynolds numbers (Re). In these results, the length of the flow separation zone is nondimensionalized by the diameter of the arterial segment (D). The results demonstrate that beyond three rings, the length of the flow separation zone becomes virtually insensitive to the number of rings making up the stent. As a result of these observations, all subsequent simulations were performed on a three-ring stent.

Figure 15 illustrates the effect of the stent wire thickness (d/D) on the length of the flow separation zone (L/D) downstream of the stent for Re <800. Not surprisingly, the results demonstrate that the size of the flow separation zone increases with increasing Re and d/D. Although the results in Fig. 15 were obtained for a uniform inlet velocity profile, largely similar results were obtained with a parabolic velocity profile at the inlet.

When these simulations are extended to sinusoidal pulsatile flow, the flow separation zone downstream of the model stent periodically appeared and disappeared. Furthermore, as illustrated in Fig. 16, the flow separation zone attained its maximum size at the points of minimum velocity during the pulsatile cycle. Schachter and Barakat (Cited from 11:1) have also studied the effect of stent interring spacing (w/D) on the size of the separation flow zone downstream of the stent (L/D). These results demonstrated that progressively increasing w/D led to an initial decrease in L/D followed by a return to near baseline values. At a sufficiently large w/D, however, L/D became insensitive to further increases in w/D.

6.6.2 CURVED VESSEL SIMULATIONS (11)

Schachter and Barakat (Cited from 11:1) have performed three dimensional simulations of the steady flow field in the vicinity of a model stent placed within curved arterial segments of diameter D. Curvature angles of 30°, 60°, and 90° were examined, and in all these simulations, the stent was placed at the end of the curved segment. Simulations were also performed for equivalent curved vessels without a stent. Similar to the straight vessel simulations, an inlet length of two dimensional (2-D) and an outlet length of 2-D were simulated.

These simulations demonstrated that the vessel curvature leads to considerable skewness in the flow velocity profile. Consequently, the size of the flow separation

zone downstream of the stent is different along the outer and inner walls of the curved vessel. L/D was found to be larger along the inner wall than along the outer wall for small and intermediate curvature (30° and 60°). This trend was reversed, however, for large curvature (90°). The fluid motion through the vessel is described in Eqs. (11) and (12):

$$\frac{dq}{dt}+\frac{dF}{dx}=0\rightarrow q=\begin{Bmatrix}A\\u\end{Bmatrix},F=\begin{Bmatrix}uA\\1/2u^2+P/\rho\end{Bmatrix} \tag{11}$$

Where: A is a vessel area, u is mean velocity, P is pressure, and ρ is known density. There are three unknowns, so the Eq. (12) is selected to relate P and A:

$$\frac{d^2}{dx^2}\left(\frac{Eh^3}{12\left(1-v^2\right)}\frac{d^2w}{dx^2}\right)+\frac{Eh}{r^2}w=P \tag{12}$$

Equation (12) describes bending of a circular cylindrical shell as derived by Timoshenko and Woinowski-Krieger (1959). In Eq. (12): E is modulus of elasticity the wall, ν is the Poisson's ratio, hr is the wall thickness, r is vessel radius, and w is wall deflection. Here, the fourth order bending term is small compared to the first order term and can be disregarded. This led to a linear relation between pressure and the square root of the vessel area.

6.7 DESIGN CONSIDERATIONS FOR A NUMERICAL ANALYSIS OF CARDIOVASCULAR STENT (15)

$$P(x)=\beta(x)\left(\sqrt{A(x)}-\sqrt{A_0(x)}\right) \tag{13}$$

In Eq. (13): the coefficient β is based on the material properties and geometry of the section in question. To solve this equation, a "Weighted Essentially Non Oscillatory (WENO)" method was chosen based on the technique's superior ability to handle sharp discontinuities in the boundaries, initial conditions, and solution. The nonoscillatory characteristic is of importance since the pulsatile nature of blood flow may introduce spurious oscillations. The WENO scheme used a windowing method that resulted in 5th-order spatial accuracy, and a 4th order Runge-Kutta method was used for the time stepping. Flow was assumed to be one-dimensional in the *x*-direction.

Table 2 shows the design parameters that were chosen for setting up the test conditions for the model. The pressure values used represent a stent inserted at a physiologic systolic pressure of 120 mmHg with the vessel allowed to relax during diastole to a pressure of 80 mmHg. The driving pressure waveform was half of a sine wave over the first 1/3 of the total cycle with the remaining part constant at diastolic pressure. The geometry and physical properties correspond closely to accepted values for coronary arteries, and the increase in stiffness is representative of a Palmaz-type balloon expanded stent.

TABLE 1 CFD flow parameters for the symmetric large graft (21).

Inlet pressure	**kPa**	**13.3**
Outlet pressure	kPa	8.77
Pressure difference	kPa	4.55
Inlet mass flow rate	kg/s	0.439
Inlet flow speed	m/s	0.581
Outlet flow speed	m/s	2.73

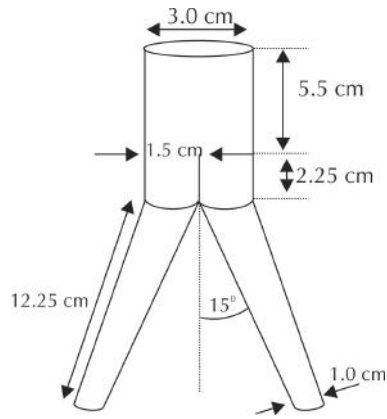

FIGURE 10 The dimensions of the base graft used in the simulations (21).

FIGURE 11 The computational domain used in the simulation (21).

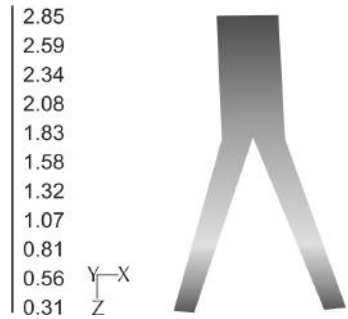

FIGURE 12 Contour plot of blood velocity on a cross-section of the graft (21).

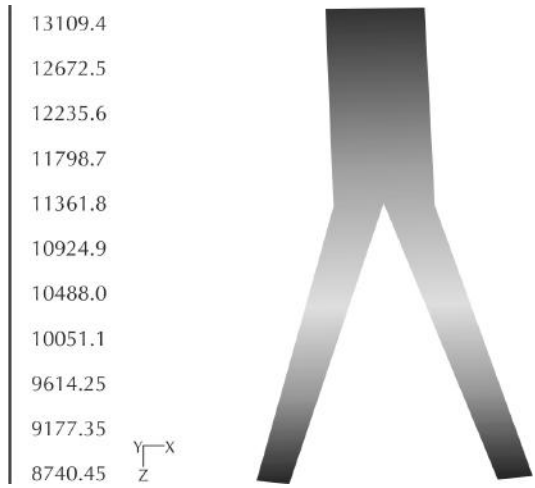

FIGURE 13 Color contour plot of static pressure on a cross-section of the flat, symmetric endoluminal graft (21).

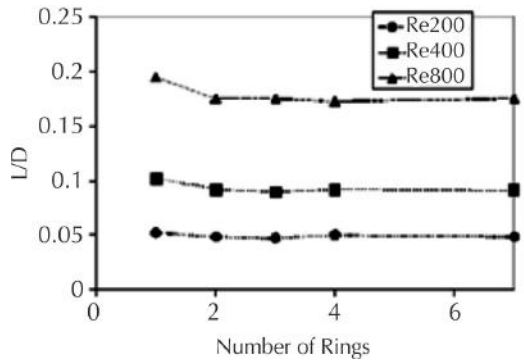

FIGURE 14 Effect of number of stent rings on L/D for w/D = 0.1 and flat inlet profile (11).

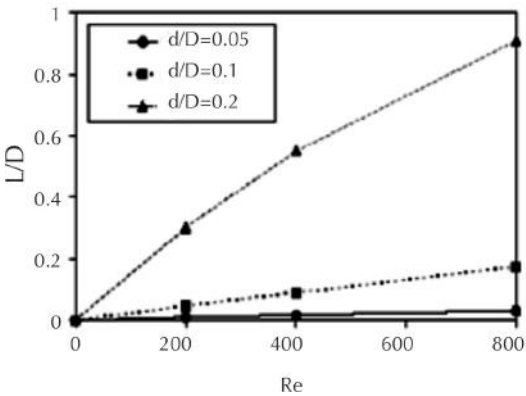

FIGURE 15 Effect of Re and d/D on L/D for w/D = 0.1 and flat inlet (11).

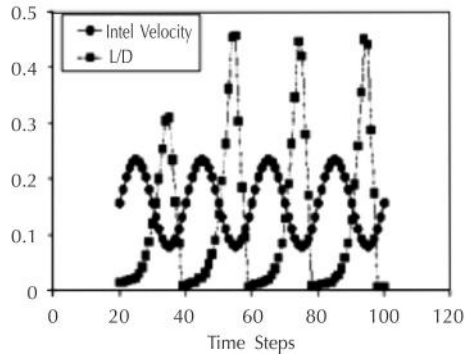

FIGURE 16 Variation of inlet velocity and L/D with simulation time steps in pulsatile flow for d/D = 0.1 and average Re = 200 (11).

TABLE 2 Initial design parameters for stent design.

Parameter	Value
Systolic pressure	0 mmHg
Diastolic pressure	–40 mmHg
Pulse frequency	1.33 Hz (80 bpm)
Base expanded radius	5.0 mm
Vessel wall thickness	0.5 mm
Stent length	5.0 cm
Vessel modulus of elasticity	10×10^5 Pa
Stent modulus of elasticity	10×10^7 Pa
Vessel Poisson's ratio	0.300
Fluid density	1000 kg/m^2

TABLE 3 Summary of the magnitudes of the pressure wave reflections for the different designs (15).

Design	Proximal (mmHg)	Distal (mmHg)
0: stenosis	–1.33–1.57	$< -0.5 < 0.5$
1: 5 mm transition	–1.61–1.88	–1.81–2.66
2: 15 mm transition	–2.04–2.39	–2.22–3.38
3: 25 mm transition	–2.50–2.88	–2.72–4.09
4: complaint center	–2.04–2.39	–2.22–3.37
5: enlarged ends	–1.82–2.15	–2.41–3.58
6: −15 mm transition	–1.27–1.48	–1.35–2.10

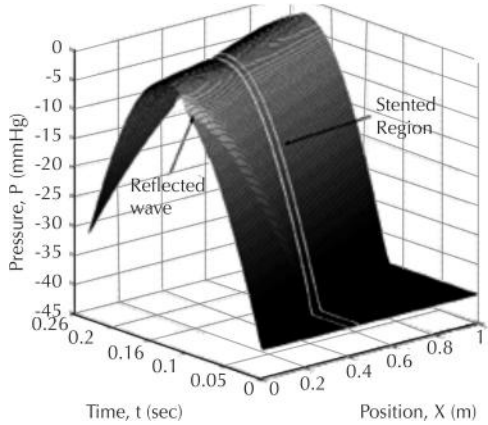

FIGURE 17 Representative pressure results for a stented region ~5 cm long with 10X nominal arterial compliance (15).

Typical results for a simulation are shown in Fig. 17. The stented region is outlined in white, and the disruption in the flow caused by the reflected pressure wave is clearly observable proximal to the stent. Similar effects are also apparent in plots of the vessel area and velocities. Six stent designs were compared and are described in Table 3. Design 0 was for a vessel with a 50% stenosis. In designs 1, 2, and 3, a several different compliance transition regions were added to the base length of the stent. Designs 4 and 5 were the same as design 2 but also included a 25% reduction in stiffness in mid stent or a 25% area enlargement. Design 6 subtracted the compliant region from the overall length. In order to measure the magnitude of the changes in pressure caused by the stent, the pressure wave as calculated for a reference vessel was subtracted from the data for the stented case. The results of this procedure are shown in Figs. 18 and 19, and Table 3. The results show that the stent introduces flow disruptions comparable in magnitude to the original stenosis, and the severity of the reflections increased with the total stent length. Designs 2 and 4 show that the wave reflection is governed by the stiffest section of the stent and not by any variation in compliance in middle of the stent. Also, enlarging the ends resulted in little benefit. The only design that showed improved behavior was number 6, which had the shortest total length.

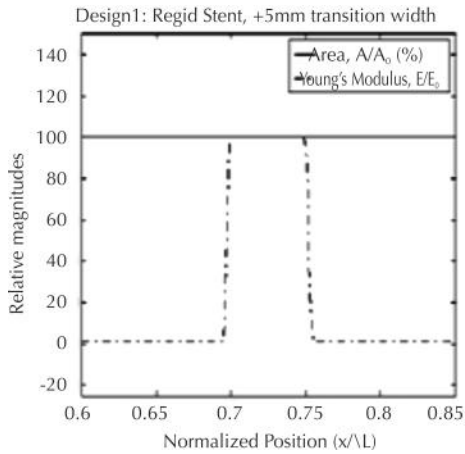

FIGURE 18 Design case 1: Area (solid) and elasticity (dashed) profiles (15).

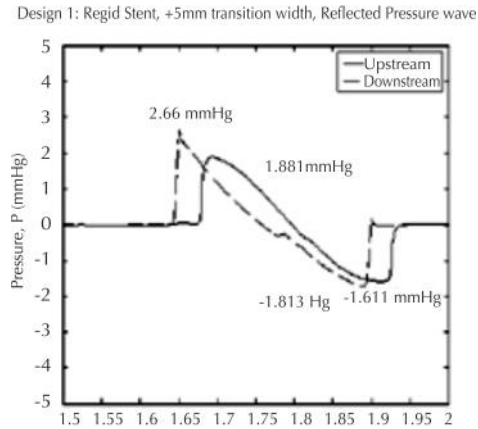

FIGURE 19 Design case 1: Upstream (dashed) and downstream (solid) reflected pressure waves (15).

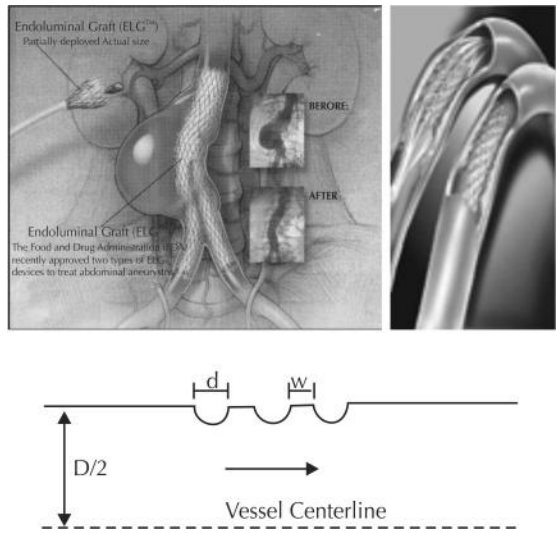

FIGURE 20 Schematic of geometry within which the simulations are performed (10).

6.8 NUMERICAL SIMULATION OF FLUID MECHANICAL DISTURBANCE INDUCED BY INTRAVASCULAR STENTS (10)

Although intravascular stents are commonly used in vascular interventions, arterial restenosis often occurs even in stented vessels. The placement of a stent in an artery causes extensive endothelial damage, and rapid repair of this injury may be essential to minimize the incidence of restenosis. The rate of endothelial wound healing may be modulated by the local flow field at the site of injury. Specifically, regions of disturbed flow may retard the process of wound repair. Researchers have used CFD to investigate the steady and pulsatile flow field in the vicinity of model stents placed within straight arterial segments and have focused on the occurrence of disturbed flow patterns due to the presence of the stent. Barakat and Cheng (Cited from 10, 1) demonstrated the existence of a region of flow separation immediately downstream of the stent. The size of this region increases with both Reynolds number and stent wire thickness. Furthermore, this region is larger for a uniform inlet velocity profile than for a parabolic profile. In pulsatile flow, the flow disturbance takes the form of large flow reversal areas that periodically appear and disappear during the course of the pulsatile cycle. If disturbed flow affects the rate of vessel restenosis in vivo, then the results have implications to the optimization of intravascular stent design.

In its advanced stages, atherosclerosis results in lesions that protrude into the arterial lumen leading ultimately to vessel stenosis and obstruction of blood flow. The pathological complications of atherosclerosis, namely heart attacks and strokes, are the leading cause of mortality in the western world. A common interventional procedure against vascular stenosis is transluminal angioplasty where a balloon catheter is introduced into the stenosed vessel and the balloon inflated at the stenosis site to restore blood flow. The major drawback of transluminal angioplasty is a restenosis, a complex process that generally occurs over a period of few months and that leads to

recurrence of vessel stenosis. About 30% of subtotal lesions and 50% of total occlusions restenose.

Intravascular stents are devices that were initially developed with the hope of significantly decreasing the incidence of restenosis following angioplasty. Stents are coil-spring expandable wire meshes that are introduced in a compressed state into a diseased artery and expanded against the arterial wall at the site of stenosis (Fig. 23) or occlusion to create a false lumen through which blood flows. In addition to restoring blood supply, stents are intended to both provide structural support to the wall of the diseased artery and to physically hinder the occurrence of restenosis. The overall effectiveness of stents remains controversial. While several clinical trials have demonstrated that stenting may be more effective than angioplasty in maintaining long-term vessel patency and in reducing the incidence of restenosis, other studies suggest that the long-term prognosis of patients receiving stents may not be very different from those undergoing only angioplasty.

It is likely that the rate of repair of endothelial injury following stent placement is affected by the local fluid mechanics in the vicinity of the stent. In vitro, fluid mechanical forces have been demonstrated to intricately regulate endothelial cell structure and function. More specifically, endothelial cells exposed to large spatial gradients of shear stress migrate away from these gradients, while cells exposed to relatively small shear stress gradients do not exhibit such behavior. If similar responses occur in vivo, then repair of endothelial injury in the vicinity of a stent may be relatively slow in regions of large shear stress gradients thus rendering these regions more likely to restenose. What type of fluid mechanical conditions is needed to generate such large shear stress gradients? One possibility is the occurrence of a flow separation zone where the shear stress gradients at the points of boundary layer separation and reattachment are particularly large.

Barakat and Cheng (Cited from 10:1) have investigated the conditions necessary for the occurrence of flow separation in the vicinity of an intravascular stent using CFD. They expected that a number of geometric and flow parameters play a role in determining whether or not flow separation occurs, and CFD analyzes provide a versatile tool for probing the effect of each of these parameters on the flow field and resulting wall shear stress distribution.

6.8.1 GEOMETRY AND FLOW MODELING (10)

In CFD simulations, stents are idealized as a series of rigid rings that are positioned within straight, rigid-walled arterial segments. The computations are performed assuming two-dimensional (axisymmetric) geometries under both steady and pulsatile flow conditions. A schematic of the simulated geometry is illustrated in Fig. 20. In Fig. 20: ‘d’ denotes the simulated stent wire thickness, ‘w’ the stent interring spacing, and ‘D’ the diameter of the modeled arterial segment. The fluid in all the simulations is assumed Newtonian fluid with properties that approach those of blood: density, ρ = 1060 kg/m^3 and dynamic viscosity, $\mu = 3.5x10^{-3}$ kg/m-s.

6.8.2 COMPUTATIONAL METHODS (10)

The solutions of the governing Navier-Stokes equations for the axisymmetric geometries modeled are obtained using the commercially available CFD code NEKTON (Fluent, Inc., Lebanon, NH). NEKTON is a spectral element code with powerful post-processing capabilities. In NEKTON, the governing flow equations are discretized in space according to the spectral element method. Spectral elements combine high order (spectral) accuracy with the geometric flexibility of low-order finite element methods.This method is described in detail by Fluent Inc., but briefly, the computational domain is divided into a number of nondegenerate spectral elements within which all information on geometry, flow initial and boundary conditions, and solutions is approximated by high order polynomial expansions. A local mesh is constructed within each element, and points on this mesh are used as interpolant points for the expansion of all dependent variables.

Discrete equations are generated by inserting assumed forms of the dependent variables into the governing equations and requiring that the residual vanish in an integral sense. The computed numerical variables correspond to values occurring at the interpolant points of the mesh. Convergence is obtained by increasing either the number of spectral elements or the number of interpolant points in each element.

Both steady and pulsatile flow simulations can be performed with emphasis on flow disturbance in the vicinity of the modeled stent. The results of these simulations are described as follows: Under most of the conditions studied and for steady flow, the presence of the stent within the flow field resulted in a region of boundary layer separation and flow recirculation immediately downstream of the stent. However, the size of this recirculation flow zone depended on the various flow and geometric parameters considered.

TABLE 4 Differences between aneurysm and stenosis.

Parameter	Aneurysm	Stentosis
Definition	An aneurysm is dilatation of the wall of a artery due to defect in the wall.	Narrowing of a hollow organ resulting in the reduction of the diameter of the organ. It can be a vessel or viscera
Volume	Same	Same
Flow Rate		
Flow	Decreases	Increases
Velocity		
Fluid	$V \alpha 1/p$	$V \alpha 1/p$
Pessure	Therefore, P increases.	Therefore, P decreases.
Kinetic Energy	$KE = ½ m v^2$	$KE = ½ m v^2$
	Therefore $KE \alpha v^2$	Therefore $KE \alpha v^2$
	Therefore KE inreases.	Therefore KE inreases.

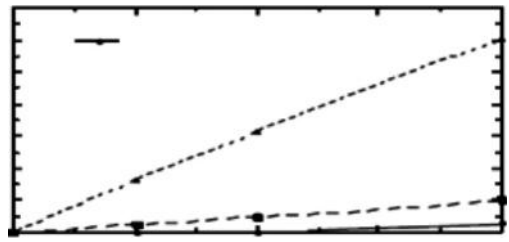

FIGURE 21 Effect of flow Reynolds number (Re) and stent wire thickness (d/D) on the length of the flow separation zone immediately downstream of the stent (10).

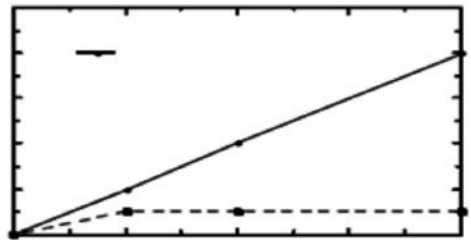

FIGURE 22 Effect of the shape of the velocity profile at the flow inlet on the length of the flow separation zone immediately downstream of the stent (10).

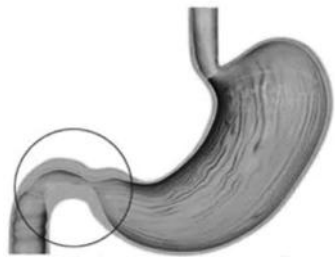

FIGURE 23 Stenosis (20).

Table 4 indicates differences between stentosis and aneurysm. Figure 21 illustrates the effect of flow Re and stent wire thickness (d/D) on the length of the flow separation zone downstream of the stent (expressed in dimensionless form as L/D). In these simulations, the velocity profile at the flow inlet was assumed to be uniform (plug flow). Figure 22 illustrates the effect of the shape of the velocity profile at the flow inlet on the length of the flow separation zone immediately downstream of the stent.

The results demonstrate that the size of the flow separation zone increases with both Re and d/D. In fact, for the thinnest-wire stent considered (d/D = 0.05), flow separation did not occur at the lower values of Re studied (Re = 200 and 400) but did occur at Re = 800. Wall shear stresses within the flow separation zones were considerably lower than outside these zones; the peak wall shear stress within the recirculation zone was typically less than one fifth of that outside the flow separation region. On the other hand, the spatial gradients of wall shear stress were largest in the immediate vicinity of the flow separation and reattachment points.

6.8.3 PULSATILE FLOW (10)

The steady flow results above provide valuable insight into the impact of various flow and geometric parameters on the flow field in the vicinity of an intravascular stent. However, these are not physiologically relevant. Blood flow in large arteries is highly pulsatile, and pulsatile flow patterns have been shown in various experimental and computational studies to deviate considerably from those in steady flow. Barakat and Cheng (Cited from 10, 1) have extended their simulations to pulsatile flow. In these simulations, the temporal variation of the pulsatile waveform was idealized as a nonreversing sinusoid with a frequency of either 1 Hz (angular frequency of 2π) representative of resting conditions or 2 Hz more typical of exercise conditions. Thus, the inlet velocity profile was assumed to be a temporally sinusoidally varying uniform profile so that the Reynolds number had the form: $Re(t) = Reo(1+\cos\omega t)$, where Reo corresponds to a representative Re value in the arterial system and ω was either 2π or 4π.

6.9 FRICTION IN STENTS

Friction in stents can be significant so that it does not slide from its specific place in the artery (39). Friction can also be a disadvantage because it is very difficult to deploy it in the artery (39). In the deployment of a stent, it is difficult to advance a balloon catheter as more friction between the wire and the vessel wall exists in a small vessel (39). Therefore, very low profile balloons are frequently used. Deployment of stents in small vessels may be more challenging. As friction is increases, the advancement of a stent becomes more difficult. The lesions may be localized in more distal segment (39). In – vitro experiments have shown that stents (without side holes, those made with material with a low coefficient of friction or containing a hydrophilic coating) resist bacterial colonization at sites of surface irregularity and sludge formation because they are not as smooth as one would like (17). Coated stents have low coefficient of friction and may increase stent longevity. The coating provides friction reduction, which aids in the passage of the catheter through lesions in blood vessels (51). To reduce friction and thrombogenicity, Teflon heparin coatings are used. Hydrophilic polymer coating further reduces friction to advance catheters more easily into peripheral vessel branches (4).

6.10 CFD SIMULATION OF BLOOD FLOW IN THE HEART (31)

The Bloodsim project was started in September 1998 at Wake Forest University School of Medicine and lasted for 36 months. The partners were from a multidisciplinary team consisting of experts in both stress analysis and CFD, clinical scientists as well as dedicated end-users. The latter group was used to deal with cardiac prostheses in clinical practice. In the past years, the delicate issue of mechanical heart valve failure in the patient's body has often been in the news. Profound research has brought to light that incidents of this type are caused by a faltering opening and closing mechanism of the disc occluder. The project team therefore worked on a better understanding of the quantitative factor in the behavior of existing disc valves.

As a result, the partners offered the essential analytical facility to provide designers of new prostheses with the missing link in their concept. The search for a compu-

tational solution automatically leads to other domains in the cardiovascular discipline. These require urgent attention, such as the interaction of the blood flow with implanted devices, artificial vessels or even with a complete mechanical heart. Use of the simulation tool might even be extended to different areas within the human body that are submitted to similar kinds of problems. The aim is to create a commercially available CFD code as well as an authoritative stress analysis package for the health care market, which integrate the complementary functions to tackle all current cardiovascular complications in a simulation environment.

Cardiovascular simulation not only relates to the behavior of the blood as a heterogeneous, anisotropic and nonNewtonian fluid, but also to the typical boundaries of the flow, which are constituted by the flexibility of the arteries, veins and heart. This implies that the use of simulated rigid walls and fixed approximations of probable boundary motion are not easy to predict the course of the blood. Indeed, it often occurs that the flexible natural boundaries have a pronounced effect on the flow. The simulation tool therefore takes into account all these factors to offer clinicians a genuine insight in different mechanisms that are involved in the cardiac process and to help manufacturers in the design of perfectly functioning prostheses.

6.10.1 TURBULENCE MODELING FOR PULSATILE TRANSITIONAL FLOWS (31)

A major difficulty in the prediction of flows in the carotid arteries involves correctly accounting for the transitional nature. Ad-hoc treatments of natural transition that have proved effective elsewhere (e.g., prescribing the location of the transition point as a function of Re_\theta) are inappropriate in these confined flows, especially when stenoses – leading to the formation of free jets – are involved. Here we discuss ongoing efforts to develop a viable method for analysis of transition nature in arterial flows within the framework of two-equation models of turbulence. One strand of this effort involves coupling a “low Reynolds number k-\epsilon model” to an equation governing the transport of intermittency.

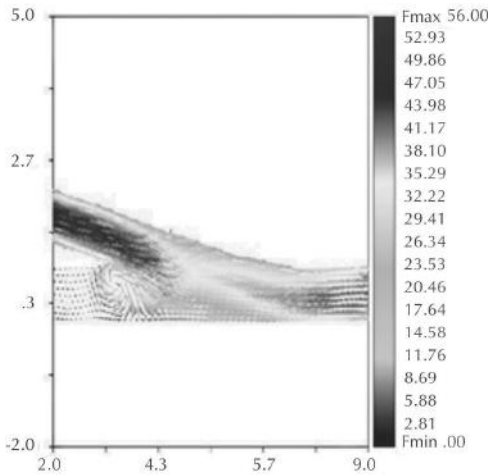

FIGURE 24 Flow field in a 2D anastomosis (38).

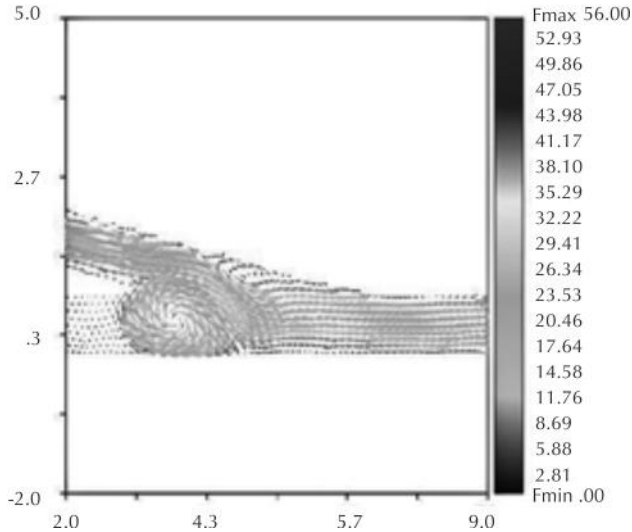

FIGURE 25 Flow field in a 2D anastomosis (38).

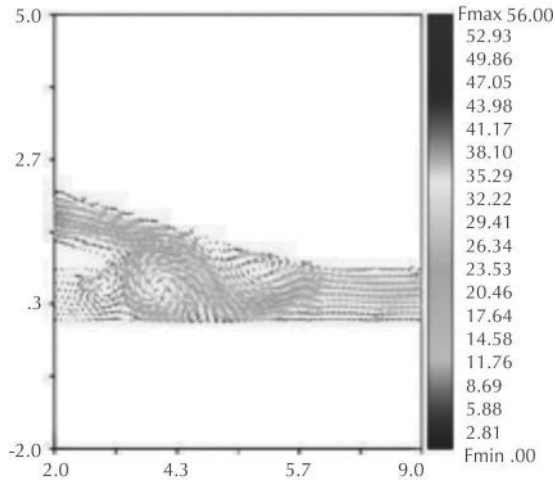

FIGURE 26 Flow field in a 2D anastomosis (38).

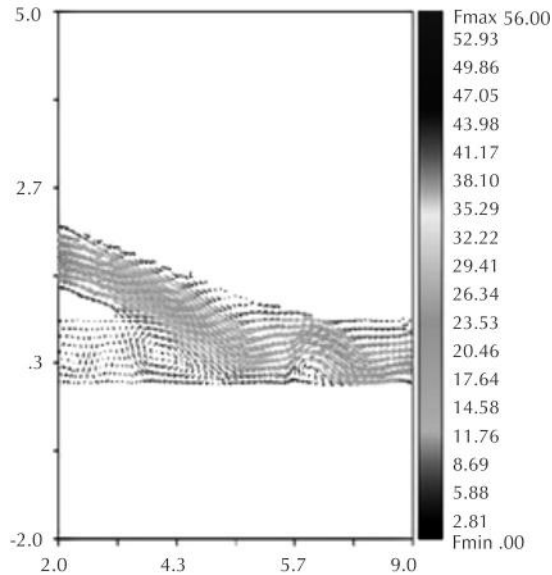

FIGURE 27 Flow field in a 2D anastomosis (38).

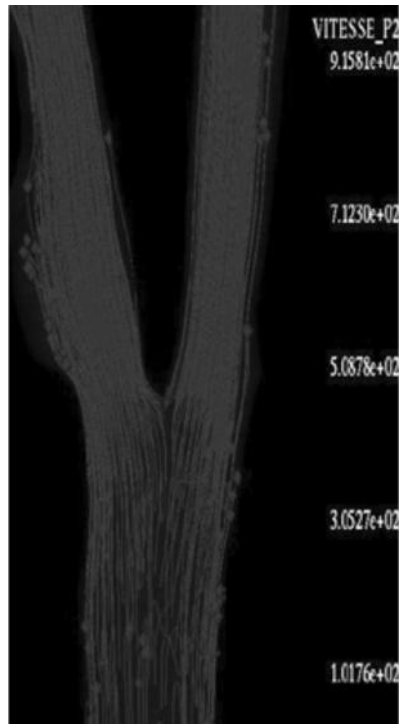

FIGURE 28 Blood flow patterns (38).

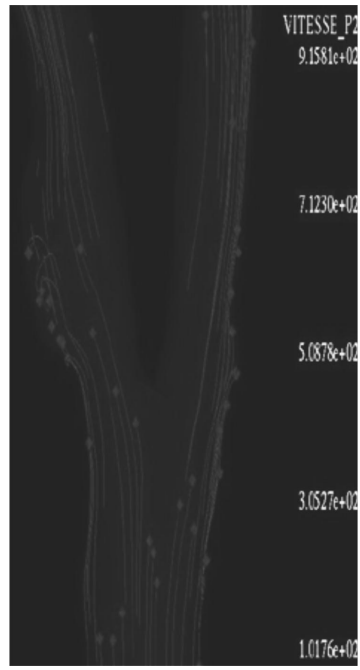

FIGURE 29 Blood flow patterns (38).

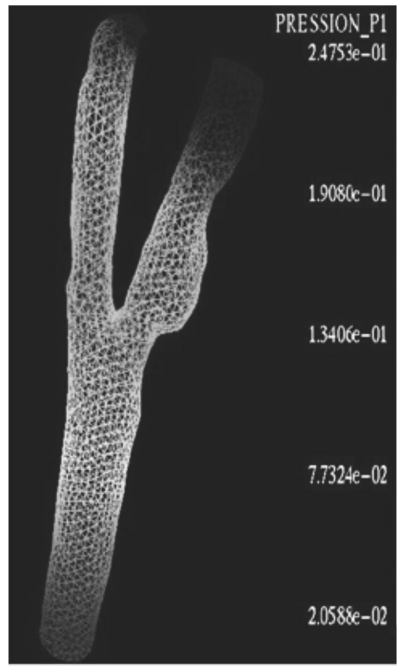

FIGURE 30 Pressure locations in a carotid bifurcation (38).

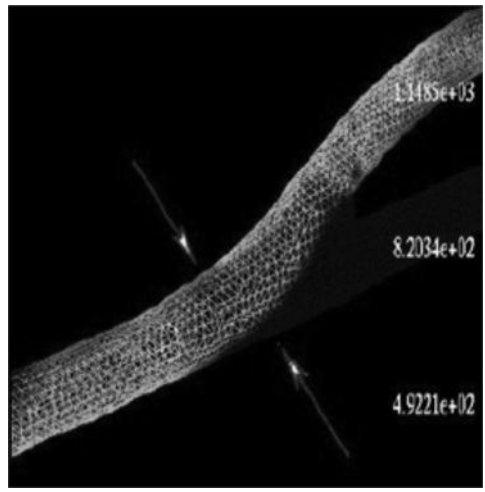

FIGURE 31 Shear stress computation (38).

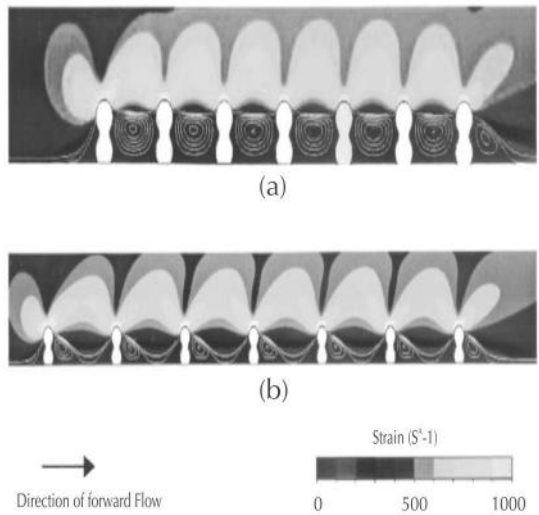

FIGURE 32 Stented artery mechanics and restenosis (45).

Alternative proposals for closing this equation are assessed in relation to data from fully developed pipe flow in the transitional regime. Further, a time-dependent flow rate is prescribed having a waveform characteristic of that found in a severely stenotic artery. Conclusions are drawn regarding the validity of this approach, and its ability to reproduce observed variations in wall shear stresses.

Fluid dynamics of blood in arteries plays a crucial role in the genesis, development and prevention of cardiovascular diseases (38). Computational hemodynamics has become an useful tool to evaluate the behavior of blood flowing through natural vessels

or artificial prosthesis and an accurate knowledge of the local flow field is important to prevent possible damage. The aim of this research unit is to solve local and global blood flow problems, and develop computational method for simulating vascular flow (38). Recirculation zones during four different instants of the heart beat are described in Figs. 24 to 27 (38). Flow patterns in the previous Carotid Bifurcation during two different instants of the heart beat are shown in Figs. 28 and 29 (38).

6.10.2 UNSTEADY FLOW ANALYSIS OF SACCULAR ANEURYSMS IN THE BASILAR ARTERY (45)

The distribution of normal and shear stresses on the wall a saccular aneurysm formed in the basilar artery have been measured using Particle Image Velocimetry (PIV) techniques. The effects of blood pressure, cardiac rate, and Reynolds number on the flow characteristics have been investigated over a wide range of geometries using a flow model. The results are analyzed for three-dimensional vortical structures typically formed in these flows. Furthermore, the effect of placing stents of varying porosity on the shear stresses along the aneurysm wall has also been investigated. Geometrical reconstruction and mesh of a REAL carotid bifurcation (starting from Computed Tomographies) is shown in Fig. 30 (38). Three-dimensional anastomosis reconstructed by a glass model and shear stress computation is shown in Fig. 31. The arrows indicate the low shear stress zones (46).

6.10.3 EFFECTS OF STENTS ON BLOOD FLOW PATTERNS (30)

The placement of a stent in an artery affects the details of flow adjacent to the artery wall, as well as the overall flow patterns in the artery. A typical stent strut is approximately 0.15 mm in thickness, and stents are deployed into arteries at least 3 mm in diameter. Thus, the direct effects of stent strut protrusion into the lumen are confined to a region close to the artery wall. The effects on overall flow patterns are due to structural aspects of the stent/artery wall interaction. The degrees to which these factors affect flow patterns depend strongly on stent design and stent strut configuration.

The protrusion of the stent strut into the lumen of the artery corresponds to well-known flow situations from aerodynamics classified as flow over backward or forward facing steps. In a backward facing step flow, the momentum of the fluid flowing over the step carries the fluid past the corner of the step, creating a region of flow separation. Under steady flow conditions, the fluid contained in this region does not mix with the fluid in the mainstream, thus there are implications on the transfer of blood-borne substances in these regions adjacent to stent struts. In a forward facing step flow situation, the step inhibits the forward movement of the fluid adjacent to the strut, creating a separation zone. The separation zones associated with forward facing steps are typically smaller than those associated with backward facing steps.

The placement of a stent against the artery wall creates a series of adjacent backward and forward facing steps that may interact with one another. The use of backward and forward facing steps to describe blood flow over stents is only applicable in the acute stages of implantation. There is some evidence, however, that the stent geometry is still represented in the neointimal development patterns even weeks after implantation. The effects of stent strut spacing on blood flow patterns adjacent to the artery wall

have been studied using CFD techniques. These techniques have the advantage of producing accurate information on all flow variables (velocity, pressure, shear stress, etc.) very close to the artery wall. Experimental techniques such as laser Doppler anemometry, particle imaging velocimetry, and Doppler ultrasound all suffer from significant uncertainties when measurements are being taken within the small distances close to the wall that correspond to stent struts.

The flow patterns near the struts of a wall stent are also strongly dependent on the strut spacing. The wall stent is a braided wire mesh self-expanding design. Using a commercially available CFD software package, a two-dimensional model of the wire crossover points is constructed. The bottom stent wire is assumed to be embedded by 30% of its diameter into the artery wall. Physiologic flow conditions corresponding to resting and mild exercise in the coronary arteries are applied. The flow patterns are demonstrated by plotting instantaneous streamlines and shear rate contours. Within the range of geometric parameters used to construct actual Wallstents for clinical use, the flow patterns vary tremendously. With smaller stent wire spacings (less than six wire diameters), the stagnation regions from adjacent struts merge together for the entire cardiac cycle, creating one single stagnation region. For wire spacings larger than six wire diameters, the stagnation regions are split for at least some portion of the cardiac cycle, with the flow reattaching in between.

The strong dependence of flow stagnation on stent strut spacing has also been observed by Henry (30) using a computational model. For a stent strut spacing of three strut heights, the wall shear stress between the struts was less than 18% of the smooth wall value. For a stent strut spacing of 12 strut heights, the flow reattached between the stent struts, and the wall shear stress was approximately 90% of the smooth wall value between the struts.

Henry (30) also included a simple model for arterial wall compliance, but the rigid wall results were not markedly affected. It is important to note that the strut shape did not affect the nature of the near-wall flow patterns. Berry employed a two-dimensional representation of overlapping circular wire struts, while Henry employed 500. J. E. Moore, Jr. and J. L. Berry used a rectangular cross section. In an earlier report of preliminary results, Xu and Collins constructed semicircular models of stent struts. Their velocity vectors and wall shear stress profiles agreed well with the subsequent studies of Berry and Henry (30).

This general behavior of flow stagnation associated with stent deployment was recently confirmed in a combined experimental/computational flow study by other investigators. However, the construction of their model was completely different from the models presented earlier. Their cylindrical model of flow over stent struts featured the protrusion of the artery wall between the stent struts as the primary protrusion into the flow stream. The tops of the stent struts were thus the local “low points” in the wall profile, with the struts completely embedded in the wall. The vessel wall between the struts was assumed to protrude 0.2 mm into the lumen past the tops of the stent struts in a 2.8 mm diameter artery. No justification for the use of this degree of protrusion was given.

Similar patterns of flow stagnation to those described earlier above were noted, although there were no studies of the effects of stent strut spacing. The geometric

variation that was included was a representation of the acute stage (so-called "sharp stented vessel") and a latter stage when some neointima had formed ("smooth stented vessel"). Very little difference in flow patterns was noted.

The effects of flow patterns associated with backward facing steps on vascular endothelial cells have been the subject of several studies, although none directly related to stents. Depaola (30) noted that confluent endothelial cells migrated away from the flow reattachment point in an in vitro flow chamber. Truskey demonstrated that subconfluent endothelial cells aligned with the flow direction near the flow reattachment point.

Confluent cells, however, showed no preferential alignment in this region. Heidekker employed fluoroscopic techniques to quantify endothelial cell proliferation rate in a backward facing step flow chamber. It was found that cellular proliferation was higher near the flow reattachment point than in adjacent regions. These studies demonstrate quite clearly that the flow stagnation patterns produced by stent strut protrusion into the flow stream have an effect on endothelial cell behavior.

Perhaps the most important aspect of endothelial cell behavior with regard to stents is their ability to regrow over the denuded artery wall, stent, and neointima. In an in-vitro experiment with a stainless steel strut embedded flush into a gel surface, Sprague demonstrated a clear dependence of endothelial cell migration on wall shear stress. Moore and Berry (Cited from 45:1) found that the stainless steel surface was 59% covered with endothelial cells after 7 days under static conditions, compared to 87% coverage with a shear stress of 15 dynes/cm^2 at the same time point. Walsh have reported results of endothelial cell regrowth patterns in simulated stented flow chambers in which the stent struts protruded into the flow stream. While no growth of the cells over the stent struts was observed over the experimental period of 7 days, lateral migration of endothelial cells was observed to occur at growth rates of approximately 15 mm/h.

The initial growth of the cells appeared to be along the stent strut in the flow stagnation zone, with preferential alignment with the stent strut. Once the cells became confluent, the 501 Stented Artery Mechanics and Restenosis direction of preferential alignment was with the direction of flow. Simon noted that the largest areas devoid of endothelial cells were located downstream of trapezoidal surface obstacles intended to simulate stent struts. Moore and Berry also noted that the tops of the obstacles exhibited no overgrowth of endothelial cells when the obstacles were more than 175 mm in height.

The effects of stents on arterial flow patterns may extend beyond the region very close to the stent struts, depending on a host of associated mechanical factors. The imposition of the stent geometry on the artery wall affects the overall vessel geometry, as well as the compliance of the artery. When a straight, balloon expandable stent is deployed into a curved artery, the stent will tend to straighten the artery. This geometric change was quantified, and its effects on steady flow wall shear stress, were quantified by Wentzel et al.

The actual stent mesh geometry was not represented in their study. The increases in curvature at the proximal and distal ends of the stent led to significant changes in the shear stresses from the base line (no stent) case. The spatial maximum wall shear

stress at the proximal end of the stent was increased by 113% with stent deployment. At the distal end of the stent, the maximum wall shear stress was increased by 30%.

The compliance mismatch at the proximal and distal ends of the stent also affects overall blood flow patterns. The abrupt changes in mechanical properties at the ends of the stent create sites of propagating pressure wave reflection. These pressure wave reflections, in addition to the abrupt changes in cross-sectional area, lead to large-scale flow disturbances. Using dye injection flow visualization, vortices were seen to form during flow deceleration. These vortices were comparable in size to the diameter of the tube, thus much larger than the stent strut thickness. Oversizing the stent by 10% did not change this behavior appreciably.

These observations have led to the design of a stent that provides a smoother transition in compliance at the ends of the stent. Prototypes of this stent, termed the compliance matching stent (CMS) were machined and deployed in the same in vitro flow visualization system as used in Berry. The development of large-scale vortices was virtually eliminated. Stents have also been demonstrated to produce small flow disturbances resembling turbulence as assessed by wall-mounted hot film probes. In this case, Palmaz and coil wire stents were deployed into a pulsatile flow producing apparatus. Under resting conditions, no flow disturbances were noted distal to the stents. The turbulent bursts appeared under simulated exercise conditions, and were greatest when stenoses were placed proximal or distal to multiple stents. Their experimental method did not allow for the measurement of flow disturbances within the stent. The production of flow disturbances by stents may also occur if the stent is deployed near a branch point and partially protrudes into the lumen due to inaccurate positioning. Stanek showed that wallstents placed across the ostium of the external carotid artery created additional flow disturbance and resistance. These phenomena could result in important clinical failures as thrombus begins to form on the stent. Fabregues noted that flow disturbances of this type were reduced if the end of the stent that protruded into the parent vessel could be beveled and positioned appropriately. The thrombogenic properties of stents may also play a role in embolus formation from adjacent stenoses, as demonstrated by Sukavaneshvar.

6.10.4 DETERMINATION OF BLOOD VISCOSITY (9)

Blood viscosity (μ) during each intervention was measured in duplicate at 37°C for six different shear rates by using a cone plate viscometer. The μ was then plotted against shear rate, and relations describing a three-constant exponential decay were obtained for each intervention by using Marquardt-Levenberg algorithm.

6.10.5 ESTIMATION OF LOCAL BLOOD FLOW VELOCITY AND SHEAR RATE (9)

Local blood flow velocity was determined 1–3 mm proximal and distal to the implanted stent at the epicardial and myocardial luminal surfaces of the Left Anterior Descending coronary artery (LAD). Doppler pulse penetration depth was monitored by digital readout of the Doppler module adjustable focus depth. Digitized sample volumes (~0.23 mm^3) were obtained at a minimum of 14 axial depths across the vessel and converted to velocity by using the equation = $(2f^*c)/(fO \cos \theta)$, where is the blood

velocity, f is the Doppler frequency shift, fO is the initial frequency of the ultrasonic pulse, *c* is the wave speed, and is the piezoelectric crystal insonation angle. Doppler penetration depths rendering zero blood flow were assumed to be indicative of the epicardial and myocardial luminal surfaces. Velocity waveforms at each axial depth were ensemble averaged (Fig. 33A) and spatially aligned to reconstruct velocity profiles (Fig. 33B) for each intervention. Least squared interpolation was then performed to acquire near wall velocity, assuming no slip at the vessel wall. Wall shear rate (γ_u) was also calculated by using a finite difference method (See Fig. 33c) that allowed determination of localized estimations from blood flow velocity measurements at the epicardial and myocardial luminal surfaces of the LAD proximal and distal to the implanted stent by using the differential equation $\gamma_u = \partial u/\partial r$, where $\partial u/\partial r$ is the partial derivative of the velocity magnitude with respect to the radial position (r).

6.10.6 DETERMINATION OF REGIONAL AND LOCAL SHEAR STRESS (9)

Regional (τ) and local shear stress (τ_u in Fig. 33D) for each time point in the cardiac cycle were calculated as the product of the measured in vivo viscosity and the regional or local shear rate. Oscillatory shear stress (τO_s) was determined as the magnitude of the waveform. The rate of oscillatory shear stress (τO_s) was calculated as the product of τO_s and heart rate.

Intimal hyperplasia within a stented region of the coronary arteries remains a significant problem in 15–20% of patients. A number of studies have extensively examined the time course and physiological mechanisms of vessel restenosis after stent placement, but the role of changes in coronary fluid dynamics in this process has not been thoroughly investigated. Alterations in coronary hemodynamics within the stented region may contribute to restenosis concomitant with vascular injury sustained during implantation. Tissue responses resulting from stent implantation may persist for up to 3 months after the intervention and vary with stent type. In addition, recent evidence suggests that τ_u distributions during this time may influence vascular smooth muscle cell response to the sustained vascular injury. The geometry of the involved vessel is an important factor that influences shear stress distributions, and regions of maximal intimal thickening have been strongly correlated with areas of low wall shear stress and deviations of the principal τ_u vector from the prominent flow direction in other arterial vascular beds. Intimal hyperplasia has also been shown to occur in regions of low shear stress proximal and distal to a stent, suggesting that altered shear stress distributions may contribute to restenosis in these areas after stent deployment. The impedance mismatch between an implanted stent and the native artery may lead to secondary flow and contribute to neointimal hyperplasia. Stent implantation likely causes alterations in spatial and temporal wall shear stress gradients, which have been associated with altered membrane fluidity and proliferation in isolated endothelial cells. Taken as a whole, these data support the hypothesis that changes in fluid dynamics due to stent geometry may be risk factors for restenosis. Importantly, studies conducted to date have evaluated the impact of stents on fluid dynamics under steady-state conditions but not during increases in blood flow resulting from exercise or exogenously administered vasodilators.

This study investigates the role of changes in coronary fluid dynamics during vasodilation in the presence and absence of a coronary stent. The results indicate that stent implantation produces a modest increase in coronary blood flow concomitant with a reduction in coronary vascular resistance. Increases in regional wall shear stress and wall τO_s observed after stent placement can be attributed to the increase in coronary blood flow because viscosity was constant for the duration of the experiments. Regulation of coronary artery blood flow occurs at the arteriolar level under normal conditions. Mechanical stimulation of the normal endothelial barrier during stent implantation may have produced modest coronary vasodilation by a nitric oxide-mediated mechanism or by prostacyclin release by remnant endothelial cells, resulting in increases in coronary blood flow and shear stress. Increases in Re, De, and Re_s indicate that blood flow in the LAD remains laminar after stent implantation but that secondary flow could be potentiated.

The results also indicate that stent implantation alters the fluid dynamic responses of the coronary artery to pronounced vasodilation. Adenosine-induced reductions in coronary vascular resistance and increases in Re, De, and indexes of were attenuated after the stent was deployed. Re and De were lower in the presence of adenosine after stent implantation, suggesting that the stent attenuated skewing of the laminar axial velocity profile toward the epicardial luminal surface of the vessel and reduced secondary flow at the myocardial wall, an observation that was occasionally noticed during velocity profile reconstruction after stent implantation. Interestingly, the magnitude of adenosine-induced LAD coronary blood flow velocity waveforms proximal and distal to the stent was less pronounced and contained more transients during end diastole than those in the absence of the stent, suggesting that the impedance mismatch between the implanted stent and native artery may be maximized during pronounced vasodilation and that the transients in these waveforms may be due to reflected waves or secondary flow within the stented region of the vessel. In contrast, adenosine-induced increases in Re_s were similar after stent placement, implying that increases in secondary flow during profound coronary vasodilation were similar in the absence and presence of the stent. Attenuation of indexes of after stent implantation during administration of adenosine suggests that the stent partially inhibits flow within this region of the vessel, resulting in localized regions of low shear stress that may potentially increase particle residence time, contribute to vascular smooth muscle cell migration and proliferation, and induce intimal hyperplasia. This hypothesis remains to be tested. The results further indicate that coronary blood flow reserve is also attenuated in the presence of a stent. Increases in coronary flow reserve after placement of coil or slotted-tube stents have been previously described in patients with coronary artery stenoses. However, the present results in dogs with normal coronary arteries suggest that the presence of a slotted-tube stent impedes coronary compliance within this vascular segment. This paradox is likely due to the difference between placing a stent in a healthy vessel as opposed to a calcified vessel and elucidates changes in the mechanical properties within this vascular segment after stent implantation.

Adenosine infusion resulted in decreased Poiseuillean resistance and compliance within the stented region before stent implantation. Similarly, Poiseuillean resistance within this region decreased after stent implantation but was greater than during the

adenosine intervention before stent implantation. Also, the compliance of the stented region was effectively reduced to zero after stent implantation in the presence or absence of adenosine. These results suggest that hemodynamic alterations secondary to resistance and compliance differences (i.e., impedance mismatch) between stented and native regions of the LAD may depend on the ability of the stented vessel to dilate, a vascular property that is limited by the mechanical and geometric characteristics of the stent.

The research demonstrates that adenosine-induced alterations in τ_u at the epicardial and myocardial surfaces proximal and distal to the stent were unchanged after the stent was deployed. These findings contrast to some degree with the results of computational models and flow visualization studies. The Doppler method used in this investigation has been previously used to resolve differences in shear stress between the epicardial and myocardial luminal surfaces, but its efficacy in assessing τ_u distributions immediately proximal and distal to the stented region of a coronary artery has not been specifically evaluated.

The results should be interpreted within the constraints of several potential limitations. Stent implantation was performed in a retrograde fashion through a snared, small distal branch of the LAD. This technique clearly differs from the antegrade introduction of coronary stents used in the cardiac catheterization laboratory and was used to minimize the extent of vascular injury associated with stent placement. However, the ligation of this small LAD branch may have affected regional coronary perfusion to some degree by producing ischemia in an area of myocardium adjacent to the stent. Nevertheless, the LAD branch remained ligated before and after stent placement, and the coronary vascular response to adenosine should not have been differentially affected by this technique. Adenosine produced decreases in heart rate, mean arterial and LV systolic pressure and $+dP/dt_{max}$ of similar magnitude before and after stent placement. However, coronary perfusion pressure remained well within the autoregulatory range, and adenosine-induced increases in coronary blood flow observed here in normal coronary arteries were similar to those previously observed when arterial pressure was restored to baseline values by using partial aortic occlusion. Thus it is unlikely that differences in indexes of fluid dynamics between stented and normal coronary arteries during administration of adenosine were related to differential actions on systemic hemodynamics. These results were obtained in acutely instrumented healthy dogs, and it is likely that differences in shear stress distributions observed in response to adenosine after stent implantation may be temporally affected as a result of progressive endothelialization of a chronically implanted stent and coronary artery disease. This investigation was conducted by using a slotted-tube stent, and changes in adenosine-induced coronary flow dynamics that occur with other stent geometries cannot be directly inferred from the present results. However, it would appear likely that other types of stents with similar thickness, stent-to-artery ratios, and radial strength properties might yield similar findings (29).

6.11 EFFECTS OF STENTS ON STRESSES OF ARTERY WALL (30)

The placement of a stent inside an artery has profound implications on the stresses in the artery wall. Balloon expandable stents are typically deployed with balloon pres-

sures of up to 15 atm, or more than 100 times a mean blood pressure of 100 mmHg. Given that it takes this much pressure to deform the stent out to the diameter of the artery, balloon expandable stents behave very nearly as rigid structures inside the artery. The outward force of the stent against the artery creates large, nonphysiologic stresses on the artery wall. In the case of self-expanding stents, the additional elasticity of the stent may reduce these stresses slightly, but the fact remains that there is a chronic action/reaction contact stress between the stent and the artery wall.

The analysis of stented artery wall stresses is impeded by the complexity of the artery wall, and the inherent difficulty in solving contact mechanics problems. The artery wall is a nonhomogeneous, nonisotropic, nonlinearly elastic structure that undergoes large deformations even in the absence of a stent. The presence of residual stresses, another complicating factor, has been shown to influence the prediction of artery wall stresses to a great degree. The fact that the outward force of the elastic stent counteracts the inward tendency of the artery (a contact mechanics problem) complicates the analysis of stented arteries even further.

A relatively simple model of stresses in a stented artery wall showed that the abrupt change in mechanical properties at the ends of the stent creates zones of intense stress concentration. It was also shown that it is possible to reduce these stresses by distributing the transition in mechanical properties over a distance of approximately one vessel radius (as is done with the CMS). However, the assumptions employed in this axisymmetric model, including the lack of consideration of the true contact mechanics, limit the applications of the results (39).

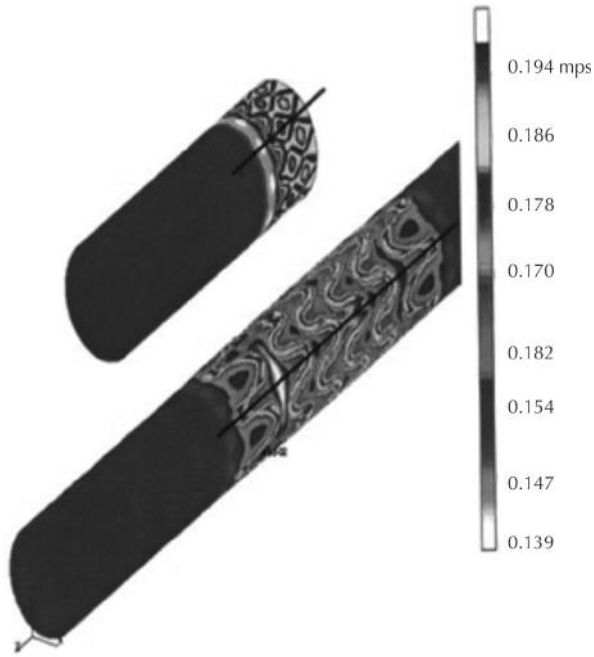

FIGURE 33 Color-encoded maximum principal stress in an artery (30).

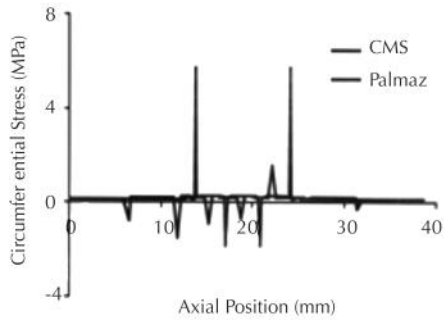

FIGURE 34 The transition in compliance reduces the maximum stress encountered by the artery wall (30).

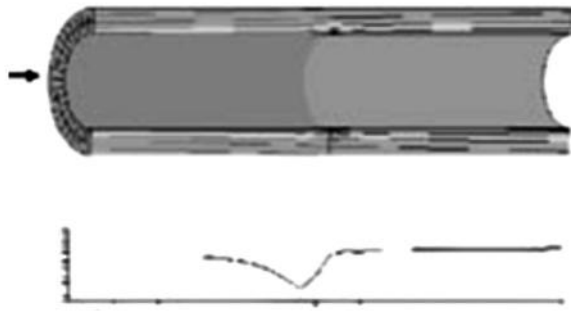

FIGURE 35 The stress distribution in the arterial-graft walls (contours) and fluid wall shear stress gradient (line plot) (30).

A more realistic study that included the true stent geometry and consideration of the contact mechanics was subsequently performed. A finite element model of an artery wall into which a Palmaz stent or CMS had been deployed was constructed using a commercially available software package. The stents were given properties representative of stainless steel, while the artery wall was modeled as a thin shell with linear elastic properties. The stresses near the ends of the Palmaz stent reached 5.5 N/mm^2. The CMS design resulted in a much lower stress at the ends of the stent, provoking a peak stress of 1.5 N/mm^2.

Rogers (30) constructed a computational model to estimate the stresses on the artery wall during balloon deployment, and found a fairly strong dependence on stent strut spacing. Higher stresses were predicted for higher balloon inflation pressures, larger stent strut spacings, and more compliant balloons. These behaviors were related to the ability of the balloon to conform to the backward facing step geometry, and the distance between adjacent struts. They included in vivo evidence that endothelial cells remain in the areas adjacent to the stent struts where the balloon should not be in con-

tact with the artery wall. This implies that direct stenting may have an advantage over angioplasty followed by stent deployment.

The adaptation of the artery wall to stent-induced stress concentration was modeled in a theoretical study by Rachev (30). Their model allowed the artery wall to build up additional tissue in response to increased stress until the stress returned to some threshold value close to the stress in the unstented portion of the vessel. Following adaptation, the artery wall thickness was greatest at the stent edge, and decreased monotonically away from the stent. Their results were similar to neointimal growth patterns observed in vivo. Figures 34 to 36 indicate stress distribution in an artery (30).

6.12 CONCLUSIONS

One cannot put any type of material in the human body. Biocompatibility must be evaluated first for any kind of material. Each of the material has its advantages and disadvantages. The majority of stents that we see in the market are of stainless steel. However, there are several materials that have been used in human body. Results may be due in part to impedance mismatching between stented and adjacent nonstented regions, as well as alterations in τ_u caused by stent implantation. Improved stent designs aimed at minimizing flow disturbances may lead to reduced vascular injury, improved stent performance, and ultimately lower rates of restenosis (54).

6.13 SUMMARY

Airways and coronary arteries can be obstructed by a variety of diseases. Airways are mainly obstructed by lung cancer, scar inflammation or weakening of the airway wall. The coronary artery obstruction is due to the high levels of cholesterol in the human body. Stents are devices that can keep open the obstructed passageway. These have emerged as effective treatments for the obstruction of airways and coronary arteries. Although their success has been outstanding, yet the patients that have received stents are vulnerable to thrombosis and restenosis. This paper includes: Applications of Fluid Mechanics in the design of the stent, the effect on the walls of the artery or the formation of balloons. This paper also presents different methods on how stents and the artery veins are studied with computational analysis with "Ansys" or "CFX" programs.

KEYWORDS

- **Aneurysm**
- **Arterial graft**
- **Artery vein**
- **Balloon**
- **Basilar artery**
- **Biocompatibility**
- **Blood**
- **Cholesterol**
- **Computational fluid dynamics**

- **Coronary artery**
- **Restenosis**
- **Stenosis**
- **Stent**
- **Stent induced stress**
- **Stented artery**
- **Stress**
- **Strain**
- **Struts and resistance**
- **Thrombosis**

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CHAPTER 7

BIOMECHANICS OF ARTIFICIAL LUNG[1,2]

CONTENTS

[1] This chapter has been modified from the review article prepared by my students (Osvaldo L. Colón, Juan A. San Miguel and Luis A. Zayas) for the course on Fluid Mechanics, INGE 4015. Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com> or visit at: http://www.ece.uprm.edu/~m_goyal/home.htm. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2] The numbers in parentheses refer to cited references in the bibliography.

7.1 INTRODUCTION

In modern days, many people suffer from respiratory diseases, including collapsing of lungs. Therefore, scientists have developed devices that can help or replace the natural lung. These devices help, partially o totally, the respiratory system to perform the function of the lungs. The purpose of the artificial lung is to oxygenate the blood. In this chapter, we discuss about the functions of the human respiratory system, biomechanics of respiratory system, components and advances of the artificial lung, and biomechanics of an artificial lung.

7.2 DESCRIPTION OF THE RESPIRATORY SYSTEM

We live because we breathe in. Inhaled breath brings life-sustaining oxygen into our body. Oxygen is the fuel that helps in the functioning of our body. Our lungs are essentially 2500 km of airways, through which oxygen is delivered to all parts of the body from the lungs, and carbon dioxide is exhaled from the lungs into the atmosphere.

The average adult at rest inhales and exhales 7 to 8 liters of ambient air per minute, which is equivalent to about 11,000 liters per day. The air that is inhaled is about 20% oxygen, and the air that is exhaled is about 15% oxygen. Therefore 5% of the volume of oxygen is consumed in each breath and converted to carbon dioxide. Therefore, a human being uses about 550 liters of pure oxygen per day. During the exercise, a person uses a lot more oxygen than this amount. One can determine how much air is moving through the lungs by exhaling into a plastic bag of known volume at each breath and seeing how long it takes to fill the bag.

Our lungs are basically a long series of tubes that branch out from our nose and mouth (from trachea to bronchi to bronchioles) and end in little thin-walled air sacs called alveoli (Fig. 1). Pulmonary capillaries are small, thin-walled blood vessels that surround each alveolus. Various gases (oxygen, carbon dioxide, and nitrogen) pass through a thin wall (about 0.5 microns thick) that is between the capillaries and the alveolus. Therefore, the air has a long journey to the lungs: past the windpipe, the vocal cords, to the lower ribs that meet in the center of our chest. From there, the windpipe branches off into the left lung and the right lung. Inside the lung, bronchi connect with tiny air sacs called alveoli. If spread out flat, all the air sacs in our lungs would cover about a third of a regular tennis court.

When we inhale, the alveoli are filled with this air. Oxygen diffuses from the air into the blood, because the oxygen concentration is high in the alveoli and low in the blood entering the pulmonary capillaries. Likewise, because the concentration of carbon dioxide is higher in the blood than in the alveolar air, carbon dioxide passes from the blood to the alveoli. The nitrogen concentration in the blood and the alveolar air is about the same. The gases exchange across the alveolar wall and the air inside the alveoli becomes depleted of oxygen and rich in carbon dioxide. When we exhale, we breathe out this carbon dioxide – enriched, oxygen-poor air. When diaphragm of our lungs expands, oxygen is pulled in. The carbon dioxide is released from the lungs during the contraction. Breathing is automatic for this highly intricate system (42).

The major function of the respiratory system is the gas exchange between the external environment and an organism's circulatory system. In humans and other

mammals, this exchange facilitates oxygenation of the blood with a concomitant removal of carbon dioxide and other gaseous metabolic wastes from the circulation. As gas exchange occurs, the acid-base balance of the body is maintained as part of homeostasis. If proper ventilation is not maintained, two opposing conditions can occur: respiratory acidosis, a life threatening condition, and respiratory alkalosis.

Upon inhalation, gas exchange occurs at the alveoli, the tiny sacs which are the basic functional component of the lungs. The alveolar walls are extremely thin (approximately 0.2 micrometers). These walls are composed of a single layer of epithelial cells (type I and type II epithelial cells) close to the pulmonary capillaries, which are composed of a single layer of endothelial cells. The close proximity of these two cell types allows permeability to gases and, hence, gas exchange. This whole mechanism of gas exchange is carried by the simple phenomenon of pressure difference. The airflow out from the lungs, when the air pressure is high inside the lungs. The air flows into the lungs flow, when the air pressure is low inside.

Airways are pipes that carry oxygen-rich air to the lungs. They also carry carbon dioxide, a waste gas, out of the lungs. The airways include: Nose and linked air passages (called nasal cavities); mouth; larynx or voice box; trachea or windpipe; and bronchial tubes or bronchi, and their branches.

FIGURE 1 Human respiratory system (17).

Air first enters the body through the **nose** or **mouth**, which wets and warms the air. The air then travels through the voice box and down the windpipe. The windpipe splits into two bronchial tubes that enter the lungs. A thin flap of tissue called the epiglottis covers the windpipe during swallowing. This prevents food and drink from entering the air passages that lead to the lungs. Except for the mouth and some parts of the nose, all of the airways have special hairs called cilia that are coated with sticky mucus. The cilia trap germs and other foreign particles in the air that enter the airways during breathing. These fine hairs then sweep the particles up to the nose or mouth. From there, they are swallowed, coughed, or sneezed out of the body. Nose hairs and mouth saliva also trap particles and germs.

Lungs and **blood vessels** deliver oxygen to the body and remove carbon dioxide from the body. The lungs lie on either side of the breastbone and fill the inside of the chest cavity. The left lung is slightly smaller than the right lung to allow room for the heart. Within the lungs, the bronchi branch into bronchioles. These tubes (bronchioles) end in bunches of tiny round air sacs called alveoli.

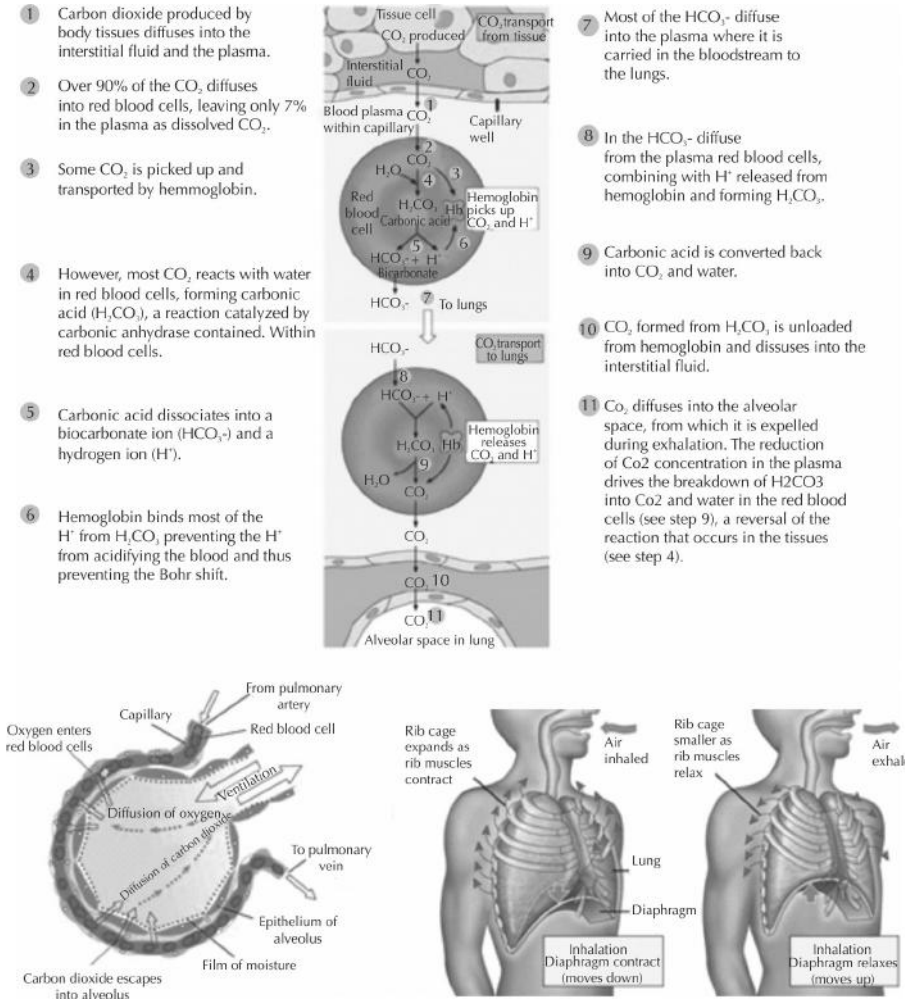


FIGURE 2 Process of inhalation and exhalation.

Each of the air sacs is covered in a mesh of tiny blood vessels called capillaries. The capillaries connect to a network of arteries and veins that move blood through the body. The pulmonary artery and its branches deliver blood rich in carbon dioxide (and poor in oxygen) to the capillaries that surround the air sacs. Inside the air sacs, carbon dioxide moves from the blood into the air. At the same time, oxygen moves from the air into the blood in the capillaries. The oxygen-rich blood then travels to the heart through the pulmonary vein and its branches. The heart pumps the oxygen-rich blood out to the body. The lungs are divided into five main sections called lobes.

Muscles near the lungs help expand and contract (tighten) the lungs to allow breathing. These muscles include the: Diaphragm; intercostal muscles; abdominal muscles; and muscles in the neck and collarbone area. The diaphragm is a dome-shaped muscle

located below the lungs. It separates the chest cavity from the abdominal cavity. The diaphragm is the main muscle used for breathing. The intercostal muscles are located between the ribs. They also play a major role in breathing. Beneath the diaphragm are abdominal muscles. They help you breathe out when the person is breathing fast (e.g., during physical activity). Muscles in the neck and collarbone area help to breathe in when other muscles involved in breathing do not work well, or when lung disease impairs the breathing. The following muscles help during the inspiration and expiration processes (Fig. 2):

	Inspiration	**Expiration**
Quiet (primary muscles)	diaphragm external intercostals	elastic recoil of lung tissue gravity on ribs internal intercostals surface tension
Forced (secondary or accessory muscles)	pectoralis major pectoralis minor serratus anterior serratus posterior superior sternocleidomastoideus scalenes upper iliocostalis	abdominals external oblique internal oblique lower iliocostalis lower longissimus rectus abdominus serratus posterior inferior

7.3 BIOFLUID DYNAMICS OF GAS EXCHANGE

The ambient air is richer in oxygen than it is in carbon dioxide. On inspiration, the inner surface of the alveolus comes in contact with the atmospheric air the lungs have inspired. The outer surface of every alveolus is in contact with a capillary. The blood in the capillary has a relative composition of oxygen and carbon dioxide that is opposite to that of atmospheric air. The alveolar walls are capillary walls and are permeable to both oxygen and carbon dioxide. Gas exchange can continue only if the respiratory system somehow reestablishes oxygen and carbon dioxide gradients between the alveoli and capillaries that surround them. In order to empty the alveoli, the medulla oblongata stops sending its signal to the diaphragm and the diaphragm relaxs. The lungs then recoil under the forces of its own elasticity. In contrast to inspiration, which is an active process, expiration is entirely passive. The recoiling process increases the pressure in the lungs and forces air out of the alveoli. See Fig. 3 for more details. Physical properties of air, oxygen and carbon dioxide are shown in Table 1.

TABLE 1 Physical properties of air, oxygen and carbon dioxide (30, 31, 32).

Property	MW	Density	Specific volume	Specific gravity	pH	Surface tension	Relative viscosity	Gas constant	Specific heat	Colloid osmotic pressure	Average volume
Units	g/gmol	g/cm^3	cm^3/g	–	NA	Dynes per cm	—	J/Kg.k	g-cal	mm Hg	ml
Air at STP	28	0.0012	869	0.0016	NA	NA	0.019	289	1004	NA	NA
Oxygen	32	0.0014	714	0.0014	NA	NA	NA	260	909 J/ Kg.K	NA	NA
Carbon dioxide	44	NA	NA	NA	NA	NA	NA	189	840 J/ Kg.K	NA	NA

7.3.1 TRANSPORT OF OXYGEN IN BLOOD

Blood is water containing a whole range of substances. It is contained in a complex network called the vascular system and is pumped around the body by our heart. Blood provides defense against diseases, and transports compounds, ions, and some elements to and from other tissues and cells. Normal blood contains about 15–16 grams hemoglobin per 100 mL. Each gram of hemoglobin can carry about 1.34 mL of gaseous oxygen. Fully saturated arterial blood will therefore contain about 20 mL of oxygen per 100 cc. The volume of oxygen in the blood is referred to as the O_2 content. Because O_2 content is dependent on the hemoglobin concentration, it does not provide a good measure of lung function. The partial pressure of oxygen (PaO_2), as measured in arterial blood, does provide an accurate picture of gas exchange in the lung. The relative amount of oxygen in the blood compared to the carrying capacity of the hemoglobin is called the oxygen saturation, and is expressed as a percentage. It is directly proportional to the PaO_2: the partial pressure of oxygen. The hemoglobin in arterial blood is only about 97% saturated with oxygen because of venous blood that passes directly through the lung (physiologic shunt). Venous blood is about 75% saturated (36).

In vertebrates, oxygen is carried by hemoglobin located in the erythrocytes (red blood cells) and stored in muscle tissue by myoglobin (Fig. 3). Hemoglobin consists of four protein subunits, each containing a nonprotein heme group. Oxygen binds to

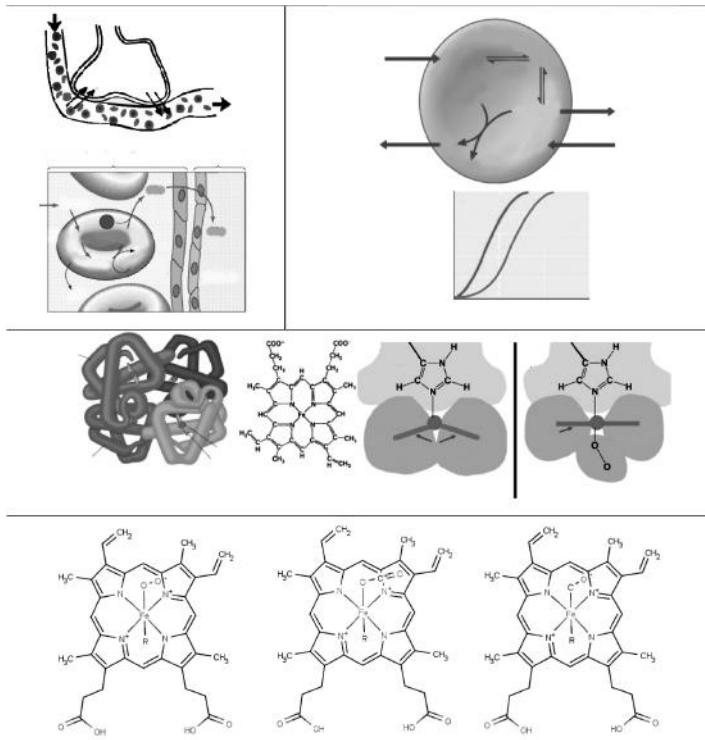


FIGURE 3 Transport of oxygen and carbon dioxide in the blood.

the heme. (Note: There are some exceptions to the presence of hemoglobin or similar molecules in vertebrate blood – the Antarctic Icefish has NO respiratory pigment at all.) Oxygen binds to the iron. This causes the iron atom to move closer to the plane of the porphyrin ring. The pulls a histidine closer to heme plane moves the alpha helical segment containing the histidine towards an adjacent helix. This movement pushes a tyrosine, which moves the C-terminal (the end of the protein chain with the COO-). In hemoglobin, the C-terminal forms an ionic bond with a positively charged residual group on an adjacent subunit, holding the subunits together. Movement of the C-terminal therefore affects the shape of the adjacent subunit and its ability to bind oxygen. Binding of oxygen to hemoglobin is cooperative. Binding of an oxygen molecule to one of the four subunits results in changes in the shape of other three subunits. Therefore, this increases the affinity of these other subunits for oxygen.

Red blood cells and hemoglobin: Oxygen is one of the substances transported with the assistance of red blood cells. The red blood cells contain a pigment called hemoglobin, each molecule of which binds four oxygen molecules. Oxyhemoglobin is formed. $Hb.4O_2$ is sometimes written HbO_8. The oxygen molecules are carried to individual cells in the body tissue where they are released (Fig. 3). The binding of oxygen is a reversible reaction.

$$Hb + 4O_2 \longleftrightarrow Hb.4O_2 \quad (1)$$

At high oxygen concentrations, oxyhemoglobin is formed, but at low oxygen concentrations, oxyhemoglobin dissociates to hemoglobin and oxygen. The balance is shown by an oxygen dissociation curve for oxyhemoglobin. This curve shows that at relatively low oxygen concentrations there is uncombined hemoglobin in the blood and little or no oxyhemoglobin, e.g. in body tissue; and at relatively high oxygen concentrations there is little or no uncombined hemoglobin in the blood, and it is in the form of oxyhemoglobin, e.g. in the lungs. In general, oxygen and carbon dioxide concentrations are expressed as partial pressures (kPa) and are termed as oxygen or carbon tension. The amount of oxygen held by the hemoglobin is called a saturation level, and is normally expressed as a percentage (Fig. 4). The oxygen dissociation curve can be used to illustrate "Law of Le Chatelier" which states that a system in dynamic equilibrium responds to any stress by restoring the equilibrium. For example, shifts in the position of the curve occur as a result of the concentration of CO_2 or changes in pH.

7.3.2 THE EFFECT OF CARBON DIOXIDE IN THE BLOOD

Haemoglobin can also bind CO_2 to form a carbaminohemoglobin, but to a lesser extent. Some of carbaminohemoglobin is carried to the lungs from respiring tissues (Fig. 3). The presence of CO_2 helps the release of oxygen from hemoglobin, and this process is called the "**Bohr effect**." This can be seen by comparing the oxygen dissociation curves when there is less carbon dioxide present and when there is more carbon dioxide in the blood (Fig. 4). When carbon dioxide diffuses into the blood plasma and then into the red blood cells (erythrocytes) in the presence of the catalyst carbonic anhydrase, most of the CO_2 reacts with water in the erythrocytes so that a dynamic equilibrium is established, as shown below:

$CO_2 + H_2O$	⟷	H_2CO_3	Carbonic acid is formed. (2)
H_2CO_3	⟷	$H^+ + HCO_{3-}$	Bicarbonate and hydrogen ions. (3)
$Hb.4O_2 + H^+$	⟷	$HHb^+ + 4O_2$	Hemoglobin. (4)

Inside the erythrocytes, negatively charged HCO_{3-} ions diffuse from the cytoplasm to the plasma. This is balanced by diffusion of chloride ions (Cl–) in the opposite direction, maintaining the balance of negative and positive ions on either side. This is called a **'chloride shift'**. The dissociation of carbonic acid increases the acidity of the blood (decreases its pH). Hydrogen ions (H^+) then react with oxyhemoglobin to release bound oxygen and reduce the acidity of the blood. This buffering action allows large quantities of carbonic acid to be carried in the blood without major changes in the pH of the blood. It is thus a reversible reaction that accounts for the Bohr effect. Carbon dioxide is a waste product of respiration and its concentration is high in the respiring cells and therefore it is here that hemoglobin releases oxygen.

Now the hemoglobin is strongly attracted to CO_2 molecules. Carbon dioxide is removed to reduce its concentration in the cells and is transported to the lungs with lower concentration of CO_2. This process is continuous since the oxygen concentration is always higher than the carbon dioxide concentration in the lungs. The opposite is true in respiring cells (8).

7.3.3 CARBON DIOXIDE TRANSPORT

Metabolism of glucose and other substrates leads to the production of CO_2 waste, therefore the cells are perpetually dumping CO_2 into the bloodstream. When CO_2 enters the bloodstream, most of it enters the red blood cells and combines with water to form carbonic acid. Some of this carbonic acid then dissociates into hydrogen ions and bicarbonate ions. The CO_2 sometimes combines also with hemoglobin.

As carbon dioxide is formed in the cells (due to aerobic metabolism), it diffuses into the plasma of the capillary. As it enters the red blood cells (which contain carbonic anhydrase), it is quickly converted to H_2CO_3, which breaks down to H+ and HCO_{3-}. About two-thirds of the HCO_{3-} will diffuse out into the plasma (and is replaced by chloride in the red cell). Only small amounts of carbon dioxide remain dissolved or attached to other compounds. About 50 mL of CO_2 gas are contained in each 100 mL of arterial blood, almost all as HCO_{3-}. As the blood goes through the capillaries, it picks up about 5 mL of additional CO_2. With this addition of acidic CO_2, the pH drops from 7.4 to 7.36. On reaching lungs, the process is reversed, and 5 mL of CO_2 is converted back from H+ and HCO_{3-} and discharged into the alveoli.

At rest, about 200 mL of CO_2 is produced and excreted through the lungs. Over 24 hr, this is the equivalent of 12,500 milliequivalents of acid produced by metabolism and eliminated through CO_2. Carbon dioxide reacts with water to form carbonic acid that then dissociates into H^+ and bicarbonate. This reaction can be catalyzed by the enzyme Carbonic An hydrase that speeds up the conversion by as much as 10 million times. Carbonic anhydrase is found inside the red blood cells but not in the blood plasma.

Why are the reactions reversed in the lungs? Bicarbonate transport across the red blood cell membrane involves simultaneous transport of chloride in the opposite

direction. This transport, by Band III protein channels, is known as the chloride shift. Oxygen releases to the peripheral tissues results in binding of hydrogen ions to hemoglobin. Lowering of H^+ concentrations results in the equilibrium of bicarbonate and carbon dioxide to shift towards more bicarbonate (36).

7.3.4 REGULATION OF RESPIRATION

The respiratory center is very sensitive to the carbon dioxide concentration in the blood, and somewhat sensitive to the oxygen concentration in the blood. When the CO_2 concentration increases, the respiratory center signals the diaphragm to increase the rate of respiration. The respiration rate in the respiration center increases due factors, such as: 1. Increase in the CO_2 concentration of the blood; 2. Increase in the concentration of hydrogen ions in the blood that lowers the pH (acidity); and 3. Decrease in the O_2 concentration of the blood. The factors 1 and 2 are most important. The reverse signals also trigger regulatory control and this leads to a decrease in the respiratory rate.

7.3.5 OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

In its most simple form, the oxyhemoglobin dissociation curve (OHGDC) is a relationship between the partial pressure of oxygen (*x*-axis) and the percent saturation of oxygen (*y*-axis). The OHGDC is an important tool for the respiration process and for understanding how the blood carries and releases oxygen. Specifically, the OHGDC relates oxygen saturation (SO_2) and partial pressure of oxygen in the blood (pO_2), and is determined by "Hemoglobin affinity for oxygen," which describes how readily hemoglobin acquires and releases oxygen molecules into the surrounding fluid (Fig. 4).

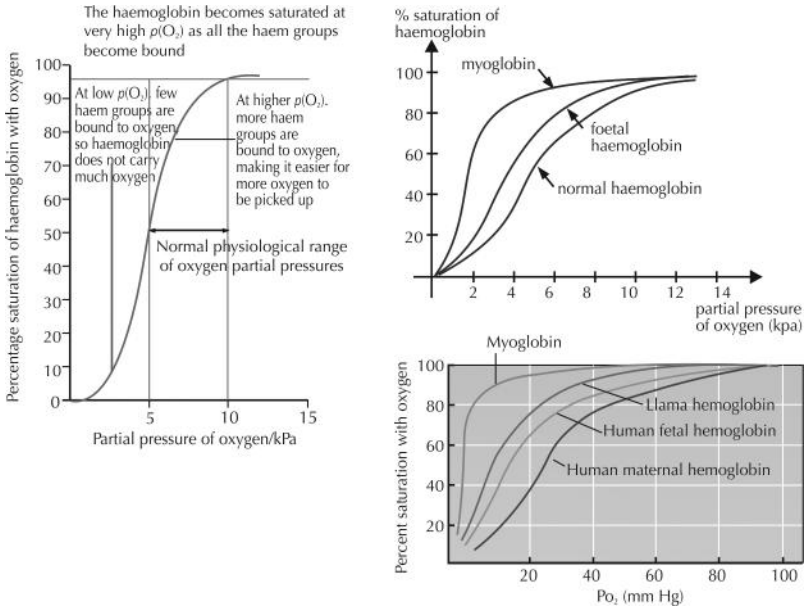


FIGURE 4 An oxygen dissociation curve for oxyhemoglobin.

A hemoglobin molecule can bind up to four oxygen molecules in a reversible way. The shape of the curve results from the interaction of bound oxygen molecules with incoming molecules. The binding of the first molecule is difficult. However, binding of the first molecule facilitates the binding of the second and third molecules, and it is only when the fourth molecule is to be bound that the difficulty increases, partly as a result of crowding of the hemoglobin molecule, partly as a natural tendency of oxygen to dissociate. Hemoglobin's affinity for oxygen increases as successive molecules of oxygen bind. More molecules bind as the oxygen partial pressure increases until the maximum amount that can be bound is reached (Peak of a sigmoid curve). As the maximum limit is approached, very little additional binding occurs and the curve levels out as the hemoglobin becomes saturated with oxygen. Hence the curve has a sigmoidal or S-shape (Fig. 4) described by the following equation:

$$S(t) = (1/(1 + e^{-t})) \tag{5}$$

At pressures above about 60 mmHg, the standard dissociation curve is relatively flat, which implies that the oxygen content of the blood does not change significantly even with large increases in the oxygen partial pressure. To get more oxygen to the tissue would require blood transfusions to increase the hemoglobin count (and hence the oxygen-carrying capacity), or supplemental oxygen that would increase the oxygen dissolved in plasma. Although binding of oxygen to hemoglobin continues to some extent for pressures about 50 mmHg, as oxygen partial pressures decrease in this steep area of the curve, the oxygen is unloaded to peripheral tissue readily as the hemoglobin's affinity diminishes. The P_{50} is a partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated, typically about 26.6 mmHg for a healthy person. The P_{50} is a conventional measure of hemoglobin affinity for oxygen. The P_{50} changes in the presence of disease or other conditions that change the hemoglobin's oxygen affinity, and consequently the curve is shifted to the right or left, accordingly. An increased P_{50} indicates a rightward shift of the standard curve, which means that a larger partial pressure is necessary to maintain 50% oxygen saturation. This indicates a decreased affinity. Conversely, a lower P_{50} indicates a leftward shift and a higher affinity.

The 'plateau' portion of the OHGDC is the range that exists at the pulmonary capillaries (minimal reduction of oxygen transported until the p ($O_{2)}$ falls 50 mmHg). The 'steep' portion of the OHGDC is the range that exists at the systemic capillaries (a small drop in systemic capillary p (O_2) can result in the release of large amounts of oxygen for the metabolically active cells).

7.3.5.1 FACTORS THAT AFFECT THE STANDARD OXYGEN DISSOCIATION CURVE

The strength with which oxygen binds to hemoglobin is affected by several factors. These factors shift or reshape the OHGDC. A rightward shift indicates that the hemoglobin under study has a decreased affinity for oxygen. This situation makes it more difficult for hemoglobin to bind to oxygen (requiring a higher partial pressure of oxygen to achieve the same oxygen saturation), but it makes it easier for the hemoglobin to release oxygen bound to it. The effect of this rightward shift of the curve increases the partial pressure of oxygen in the tissues when it is most needed, such as during

exercise or hemorrhagic shock. In contrast, the curve is shifted to the left by the opposite of these conditions. This leftward shift indicates that the hemoglobin under study has an increased affinity for oxygen so that hemoglobin binds oxygen more easily, but unloads it more reluctantly. Left shift of the curve is a sign of increased affinity hemoglobin for oxygen (e.g., at the lungs). Similarly, right shift shows decreased affinity, as would appear with an increase in body temperature, hydrogen ion (pH), 2–3-diphosphoglycerate (also known as bisphosphoglycerate) or carbon dioxide concentration (the Bohr Effect). The affinity for oxygen is affected by several factors as indicated in Table 2.

TABLE 2 Factors that affect the affinity for oxygen

Factor	**left shift (high affinity for O_2)**	**right shift (low affinity for O_2)**
Temperature	decrease	increase
2,3-DPG	decrease	increase
p ($CO_{2)}$	decrease	increase
pH (Bohr Effect)	increase (alkalosis)	decrease (acidosis)
Type of hemoglobin	fetal hemoglobin	adult hemoglobin

The shift of the curve to right or to the left depends on the status CO_2, pH, 2–3-DPG, exercise and temperature. Factors that move the oxygen dissociation curve to the right are those physiological states where tissues need more oxygen. For example during exercise, muscles have a higher metabolic rate, and consequently need more oxygen, produce more carbon dioxide and lactic acid, and the temperature rises.

a. **Variation of the hydrogen ion concentration:** In chemistry, pH is a measure of the acidity or basicity of an aqueous solution. Solutions with a pH less than 7 are acidic and solutions with a pH greater than 7 are basic or alkaline. Pure water has a pH very close to 7. The pH is defined as the decimal logarithm of the reciprocal of the hydrogen ion activity (aH+) in a solution.

$$pH = -(\log_{10}(a_{H+})) = (\log 10\ \{1/(a_{H+})\}) \quad (6)$$

A decrease in pH (increase in H^+ ion concentration) shifts the OHGDC to the right, while an increase in pH shifts it to the left. This is due to the fact that H^+ and O^2 both compete for binding to the hemoglobin molecule. Therefore, with increased acidity, the hemoglobin binds less O_2 for a given pO_2. This is called Bohr Effect. A reduction in the total binding capacity of hemoglobin to oxygen (i.e., shifting the curve down, not just to the right) due to reduced pH is called the root effect. This is seen in bony fish.

b. **Effects of carbon dioxide:** Carbon dioxide affects the OHGDC in two ways: It influences intracellular pH (the Bohr effect); and CO_2 accumulation causes carbamino compounds to be generated through chemical interactions that bind to hemoglobin forming carbaminohemoglobin. Low levels of carbamino

compounds have the effect of shifting the curve to the left, while higher levels cause a rightward shift. However, this is not the overriding effect of CO_2 accumulation. Only about 5–10% of the total CO_2 content of blood is transported as carbamino compounds. Most of the CO_2 content (80–90%) is transported as bicarbonate ions. The formation of a bicarbonate ion will release a proton into the plasma. Hence, the elevated CO_2 content creates a respiratory acidosis and shifts the OHGDC to the right.

c. **Temperature**: The temperature does not have such a dramatic effect compared to other factors, but hyperthermia causes a rightward shift, while hypothermia causes a leftward shift. Increasing temperature will weaken and denature the bond between oxygen and hemoglobin, which in turn decreases the concentration of the oxyhemoglobin.

d. **Carbon monoxide**: Hemoglobin binds with carbon monoxide 200–250 times more readily than with oxygen. The presence of carbon monoxide on one of the four-heme sites causes the oxygen on the other heme sites to bind with greater affinity. Moreover, because of hemoglobin's affinity for carbon monoxide over oxygen, carbon monoxide is a highly successful competitor. Even at minuscule partial pressures, carbon monoxide can displace oxygen and results in a shift of the curve to the left. With an increased level of carbon monoxide, a person can suffer from severe tissue hypoxia while maintaining a normal pO_2.

e. **Effects of methemoglobinaemia**: Methemoglobinaemia is a form of abnormal hemoglobin where ferrous (Fe^{2+}, normally found in hemoglobin) is converted to the ferric (Fe^{3+}) state. This causes a leftward shift in the curve as methemoglobin does not unload O_2 from Hb. However, methemoglobin has increased red blood cell affinity for cyanide, and is therefore useful in the treatment of cyanide poisoning. Nitrites can be used to oxidize hemoglobin to methemoglobin, which can then bind cyanide. This restores the ability of cytochrome oxidase to function. Furthermore, thiosulfate can be given to bind cyanide, forming thiocyanate, which can be excreted by the kidneys. Carbonic acid, H_2CO_3, dissociates to form hydrogen ions and hydrogen-carbonate ions. Undissociated carbonic acid, hydrogen ions and hydrogen-carbonate ions exist in dynamic equilibrium with one another as shown above.

7.3.6 EFFECTS OF ATMOSPHERIC PRESSURE ON GAS EXCHANGE (RESPIRATION PROCESS)

7.3.6.1 LOW PRESSURE

Because it is practically impossible to breathe a normal air at a low atmospheric pressure without immediate barotraumas, we will group these into two categories:

7.3.6.2 ACCLIMATIZATION

The effect of the low pressure on the human body depends on the temperature, because cold air is denser than warm air. For individuals that are borne and raised at altitudes of 13000 feet, the acclimatization to higher altitudes (17000 to 19000 ft.) is easier. In these cases:

- The tissue contains more mitochondria and oxidative enzymes.
- The oxygen-hemoglobin dissociation curve shifts to the right (Fig. 4).
- The oxygen carrying capacity is increased due to the increased red blood cell mass, even when the partial arterial pressure of oxygen is around 40 mm of Hg.
- The chest vital capacity is higher in relation to total body mass.
- There is a large pulmonary capillary bed.
- Pulmonary arterial pressure is higher than the sea level pressure.
- And there is physiologic hypertrophy of the right ventricle that maintains increased PA pressures despite lower pulmonary vascular resistance.
- The work capacity at 17000 feet of elevation only goes down to 87%, compared to <50% for nonacclimatized individuals.

For the nonacclimatized individuals, these altitudes produce a chronic excessively high hematocrit and sharp elevation of PA pressure with right ventricle dilatation as a consequence of hypoxic pulmonary vase-constriction and increased respiratory and heart rate. Congestive heart failure and death often occur. The body temperature and metabolism are not affected directly by low pressure. However in the acclimatized individual, a moderate increase of oxygen consumption is observed due to the increased ability of the tissue to use oxygen having more presence of oxidative enzymes (34).

7.3.6.3 DECOMPRESSION SICKNESS (34)

It can occur in nonpressurized airplane at an elevation of 30,000 feet, where the dissolved gasses in tissue begin to bubble. However, ascents <5 min rarely cause the problem. This condition occurs more readily in divers subjected to high pressures.

- Surprisingly short-lived sudden decompressions to atmospheric pressure equivalent to 50,000 feet cause no obvious harm in experimental animals or humans. When the pressure is lowered to 63,000 feet equivalent, 2.5% of the body weight evaporates from the body surface before death occurs.
- All cavities in the body at moderate altitudes can adjust, as gas escapes to the outside through the various physiologic communications (e.g., Eustachian tubes). Expansion of intestinal gas some times poses a challenge to the fast climber.
- In general, the symptoms are light-headache, nausea, reduced working capacity, confusion, pain, congestive heart failure and death (34).

7.3.6.4 HIGH PRESSURE

The pressure under sea water increases by one atmosphere for every 33 feet. Air density is directly proportional to atmospheric pressure. The effect of density is to increase resistance in the small airways increasing the work of breathing with moderate increases in respiratory rate of 5 to 10%. Mostly it affects not only the rate but also the inspiratory effort. Low-density mixtures with helium are used for facilitating ventilation of lungs with narrow airways. For a diver without scuba, the underwater pressure can reduce the chest capacity by virtue of compression of the air contained in his lungs (The squeeze) that was originally inhaled at atmospheric pressure, restriction gas exchange with the blood, and mechanically “caving in the chest” compressing vena cava with subsequent cardiovascular collapse. Scuba divers with good equipments can dive much longer. For divers on 100%, oxygen toxicity is an issue after 12 hr of use with

injury to the respiratory mucosa. When the partial pressure of inspired oxygen rises above 1500 mm-Hg, the oxygen dissolved in the blood causes toxicity (e.g., convulsions, and coma at 3 atmospheres after one hour).

If diving with compressed air at more than 150 feet, the nitrogen narcosis becomes an issue: First behaving as "laughing gas" producing joviality; and later at 200 feet acting like a general anesthetic. When significant amount of nitrogen is dissolved in blood, as an example at 200 feet, the nitrogen saturation can go up to 7 liters of dissolved gas. This resurfacing can materialize the gas creating bubbles that can cause pain, air embolism and death, thus requiring a slow stage by decompression. If breath is also held, the rapid appearance of gas in the lungs can cause barotraumas (34).

7.3.6.5 IMPORTANT OBSERVATION

Arterial pressure is measured as a "comparative difference" from the environment pressure (e.g., normal blood pressure is 120/80 mm Hg). The external pressure changes increase or reduce the absolute values of the internal pressures accordingly, but not the relative values of physiological parameters, unless a particular physiologic function is affected as in extreme cold or traumatic injury to the vascular system (34).

7.3.7 VENTILATION MODES

Since the advent of respirators, clinicians have devised a variety of strategies to ventilate the lungs based on patient conditions. For instance, some patients need a respirator to completely take over the task of ventilating the lungs. In this case, the ventilator operates in a **mandatory mode** and delivers mandatory breaths. On the other hand, some patients are able to initiate a breath and breathe on their own, but may need oxygen-enriched air flow or slightly elevated airway pressure. When a ventilator assists a patient who is capable of cemanding breath, the ventilator delivers spontneous breaths and operates in **spontaneous mode**. In many cases, it is necessary to treat the patient with mandatory ventilation. And when the condition of patient improves, spontaneous ventilation is introduced to wean the patient from mandatory breathing (24, 29).

7.4 BIOFLUID DYNAMICS OF THE RESPIRATORY SYSTEM

Matter flows from areas of high pressure to areas of low pressure. When the intrathoracic pressure is low, air (at atmospheric pressure) flows into the lung. When the intrathoracic pressure is high, air (at atmospheric pressure) flows out of the lung.

7.4.1 INHALATION

The breathing-in is usually an active movement. The contraction of the diaphragm muscles cause a pressure variation, which is equal to the pressures caused by elastic, resistive and inertial components of the respiratory system. In contrast, expiration (breathing out) is usually a passive process.

$$P = P_{el} + P_{re} + P_{in}$$

$$P = EV + R(dV/dt) + I^{*} (d^{2}V/dt) \quad (7)$$

Where: Pel = the product of elastance E (inverse of compliance) and volume of the system V; Pre = the product of flow resistance R and time derivate of volume V (which is equivalent to the flow); Pin = the product of inertance I; Second time derivate of V. R and I are sometimes referred to as Rohrer's constants.

7.4.2 THE IDEAL GAS LAW

The ideal gas law is the equation of state of a hypothetical ideal gas. It is a good approximation to the behavior of many gases under many conditions, although it has several limitations. It was first stated by B. P. Émile Clapeyron in 1834 as a combination of Boyle's law and Charles's law. The ideal gas law in its common form is given below:

$$PV = nRT \text{ or} \tag{8}$$

$PV/nT = R$

Where: R = Universal gas constant (8.314 $J \cdot K^{-1} \cdot mol^{-1}$ or 0.08206 $L \cdot atm \cdot mol^{-1} \cdot K^{-1}$) = The product of the Boltzmann constant and the Avogadro constant; P = Absolute pressure (Pascals) = $P_{gage} + P_{atm}O_{sphere}$; V = Gas volume ($m^3$); n = the amount of substance of gas (Number of moles) = mass of a gas/Moler mass; T = Absolute temperature (°K = 273.15 +°C); m = mass of a gas. At a given temperature, (pressure *x* volume) is a constant quantity. Pressure and volume vary inversely. An increase in one is associated with a decrease in the other. Universal gas constant was discovered and first introduced into the ideal gas law instead of a large number of specific gas constants by Dmitri Mendeleev in 1874. Molar form of an ideal gas law is shown below:

$$PV = (m/M)*(RT) \text{ or} \tag{9}$$

$$P = (\rho/M)*(RT) \text{ or} \tag{10}$$

$$P = (\rho)*(R_{specific}\ T) \tag{11}$$

Where: $n = (m/M)$; $\rho = (m/V)$ = Fluid density; $R_{specific}$ = Specific gas constant = (R/M). The Eq. (10) for the ideal gas law is very useful because it takes into consideration pressure, density, and temperature independent of the quantity of the considered gas. Alternatively, the law may be written in terms of the specific volume v (= the reciprocal of density) as:

$$Pv = R_{specific}*T \tag{12}$$

In statistical mechanics, the following molecular equation is given for the ideal gas law:

$$PV = NkT \tag{13}$$

Where: P is the absolute pressure of the gas measured in Pascals; V is the volume in m^3 (Note: pascal *x* m^3 = one Joule, and One Joule = 1 N-m); N is the number of particles in the gas; k is the Boltzmann constant relating temperature and energy = $1.38*10^{-23}$ $J \cdot K^{-1}$ in SI units.; and T is the absolute temperature. Comparing Eqs. (8) and (13), we

find that Nk = nR. The Table 3 indicates different forms of the ideal gas equation for a particular process.

TABLE 3 Different forms of the ideal gas equation for a particular process.

Process	Constant		Known ratio	P_2	V_2
Isobaric	Pressure		V_2/V_1	$P_2 = P_1$	$V_2 = V_1(T_2/T_1)$
	T_2/T_1		$P_2 = P_1$	$V_2 = V_1(T_2/T_1)$	
Isometric	Volume		P_2/P_1	$P_2 = P_1(T_2/T_1)$	$V_2 = V_1$
	T_2/T_1		$P_2 = P_1(T_2/T_1)$	$V_2 = V_1$	
Isothermal	Temperature		P_2/P_1	$P_2 = P_1(T_2/T_1)$	$V_2 = V_1/(P_2/P_1)$
	V_2/V_1		$P_2 = P_1/(V_2/V_1)$	$V_2 = V_1(V_2/V_1)$	
Isentropic (Reversible adiabatic process)	Entropy[a]		P_2/P_1	$P_2 = P_1(V_2/V_1)$	$V_2 = V_1(P_2/P_1)^{(-1/\gamma)}$
	V_2/V_1		$P_2 = P_1(V_2/V_1)^{-\gamma}$	$V_2 = V_1(P_2/P_1)$	
	T_2/T_1		$P_2 = P_1(T_2/T_1)^{\gamma/(\gamma-1)}$	$V_2 = V_1(T_2/T_1)^{1/(1-\gamma)}$	
Polytropic	$P*V^n$	P_2/P_1	$P_2 = P_1(P_2/P_1)$	$V_2 = V_1(P_2/P_1)^{(-1/n)}$	$T_2 = T_1(P_2/P_1)^{(1-1/n)}$
		V_2/V_1	$P_2 = P_1(V_2/V_1)^{-n}$	$V_2 = V_1(V_2/V_1)$	$T_2 = T_1(V_2/V_1)^{(1-n)}$
		T_2/T_1	$P_2 = P_1(T_2/T_1)^{n/(n-1)}$	$V_2 = V_1(T_2/T_1)^{1/(1-n)}$	$T_2 = T_1(T_2/T_1)$

[a] In an isentropic process, system entropy (S) is constant. Under these conditions, $P_1 V_1^{\gamma} = P_2 V_2^{\gamma}$, where γ is defined as the heat capacity ratio, which is constant for an ideal gas = 1.4 for diatomic gases like nitrogen (N_2) and oxygen (O_2), (and air, which is 99% diatomic). Also γ is typically 1.6 for monatomic gases like the noble gases helium (He), and argon (Ar). In internal combustion engines γ varies between 1.35 and 1.15, depending on constitution gases and temperature.

7.4.2.1 DEVIATIONS FROM IDEAL BEHAVIOR OF REAL GASES

The equation of state given here applies only to an ideal gas, or as an approximation to a real gas that behaves sufficiently like an ideal gas. There are in fact many different forms of the equation of state. Since the ideal gas law neglects both molecular size and intermolecular attractions, it is most accurate for monatomic gases at high temperatures and low pressures. Neglecting molecular size becomes less important for lower densities, i.e., for larger volumes at lower pressures, because the average distance between adjacent molecules becomes much larger than the molecular size. The relative importance of intermolecular attractions diminishes with increasing thermal kinetic energy, i.e., with increasing temperatures. More detailed equations of state, such as the van der Waals equation, account for deviations from ideality caused by molecular size and intermolecular forces. A residual property is defined as the difference between a real gas property and an ideal gas property, both considered at the same pressure, temperature, and composition.

7.4.3 DALTON'S LAW OF PARTIAL PRESSURES

In chemistry and physics, Dalton's law states that the total pressure exerted by the mixture of nonreactive gases is equal to the sum of the partial pressures of individual

gases. This empirical law was observed by John Dalton in 1801 and is related to the ideal gas laws. Mathematically, the pressure of a mixture of gases can be defined as the summation of partial pressure of each component.

$$P_{total} = \sum_{i=1}^{n}(p_i) \text{ or } P_tO_{tal} = (p_1 + p_2 + p_3 + \text{——} + p_n) \quad (14)$$

$$p_i = (P_tO_{tal} * y_i) \quad (15)$$

Where: $p_1, p_2, \text{_____}, p_n$ represent the partial pressure of each component; y_i is the mole fraction of the i-th component in the total mixture of n components; and P_tO_{tal} is the total pressure of a mixture of gases. It is assumed that the gases do not react with each other. The volume based concentration of any individual gaseous component can be determined using following equation:

$$P_i = ((P_tO_{tal} * C_i)/(1{,}000{,}000)) \quad (16)$$

Where: C_i is the concentration of the i-th component expressed in ppm. Dalton's law is not exactly followed by real gases. Those deviations are considerably large at high pressures. In such conditions, the volume occupied by the molecules can become significant compared to the free space between them. In particular, the short average distances between molecules raise the intensity of intermolecular forces between gas molecules enough to substantially change the pressure exerted by them. Neither of those effects is considered by the ideal gas model.

7.4.4 POISEUILLE'S LAW OR HAGEN–POISEUILLE EQUATION

In fluid dynamics, the Hagen–Poiseuille equation (also known as the Hagen–Poiseuille law, Poiseuille law or Poiseuille equation) is a physical law that yields the pressure drop in a fluid flowing through a long cylindrical pipe (Fig. 5). It can be successfully applied to air flow in lung alveoli or for the flow through a hypodermic needle. It was experimentally derived independently by Gotthilf Heinrich Ludwig Hagen in 1839 and Jean Louis Marie Poiseuille in 1838, and published by Poiseuille in 1840 and 1846. Therefore, it is called Hagen–Poiseuille equation in all books on fluid dynamics today.

The equation assumes: The fluid is incompressible and Newtonian; the flow is laminar through a pipe of constant circular cross-section that is substantially longer than its diameter; and there is no acceleration of fluid in the pipe. For velocities and pipe diameters above a threshold, actual fluid flow is not laminar but turbulent, leading to larger pressure drops than calculated by the Hagen–Poiseuille equation, which is shown below:

$$\Delta P = ((8\ \mu LQ)/(\pi r^4)) = ((8\ \mu LQ)/(\pi d^4)) \quad (17)$$

Where: ΔP = the pressure loss; L = length of pipe; μ = the dynamic viscosity or absolute viscosity; Q = volumetric flow rate; r = radius of a circular vessel; d = diameter; and $\pi = 3.14$. Also, we know that:

$$Q = (dV/dt) = (v^* \pi R^4) = ((\pi R^4)/8\eta)^*(\text{—}\ \Delta P/\Delta x) = ((\pi R^4)/8\eta)^*(\Delta P/L) \quad (18)$$

Where: Q = the volumetric flow rate; V(t) = the volume of the liquid transferred as a function of time; v = mean fluid velocity along the length of the tube; *x* = distance in direction of flow; R = the internal radius of the tube; ΔP = the pressure difference between the two ends; η = the dynamic fluid viscosity (Pascals-second); and L = the length of the tube.

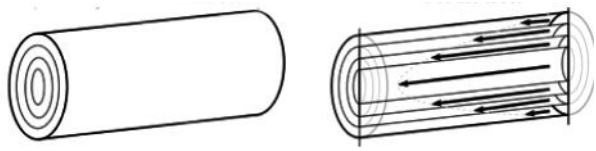


FIGURE 5 Left: A tube showing the imaginary lamina. Right: A cross section of the tube shows the lamina moving at different speeds. Those closest to the edge of the tube are moving slowly while those near the center are moving quickly.

The equation does not hold close to the pipe entrance. The equation fails in the limit of low viscosity, wide and/or short pipe. Low viscosity or a wide pipe may result in turbulent flow, making it necessary to use more complex models, such as Darcy-Weisbach equation. If the pipe is too short, the Hagen–Poiseuille equation may result in unphysically high flow rates; the flow is bounded by Bernoulli's principle. The Hagen–Poiseuille equation can be derived from the Navier–Stokes equations.

7.4.4.1 HAGEN–POISEUILLE EQUATION AND DARCY–WEISBACH EQUATION

A relationship for the Darcy friction factor in terms of the Reynolds number I shown below:

$$F_{darcy} = (64/Re) \text{ and } Re = ((\rho^* v^* 2r)/(\eta)) \quad (19)$$

Where: F_{darcy} = Darcey friction factor; Re = Reynolds number; ρ = fluid density; v = fluid velocity; r = radius of a vessel; 2r = diameter of a vessel; η = absolute viscosity; and υ = (η/ρ) = kinematic viscosity. This form of Darcy – Weisbach law approximates the Darcy friction factor, the energy (head) loss factor, for a laminar flow at very low velocities in cylindrical tube. The theoretical derivation of a slightly different form of the law was made independently by Wiedman in 1856 and Neumann and E. Hagenbach in 1858. Hagenbach was the first who called this law the Poiseuille's law. The law is also very important especially in hemorheology and hemodynamics. In 1891, Poiseuilles' law was extended to turbulent flow (when: Re>2100) by L. R. Wilberforce, based on Hagenbach's work.

7.4.4.2 POISEUILLE'S EQUATION FOR COMPRESSIBLE FLUIDS

For a compressible fluid in a tube the volumetric flow rate and the linear velocity is not constant along the tube. The flow is usually expressed at outlet pressure. As fluid is compressed or expands, work is done and the fluid is heated and cooled. This means that the flow rate depends on the heat transfer to and from the fluid. For an ideal gas in the isothermal case, where the temperature of the fluid is permitted to equilibrate with

its surroundings, and when the pressure difference between ends of the pipe is small, the volumetric flow rate at the pipe outlet is given below:

$$\Phi = dV/dt = v*(\pi R^2) = (\{\pi R^4/8\eta L\}*((P_i + P_0)/2PO\}), \text{ or}$$

$$= (\{\pi R^4/16\eta L\}*(\{(P_i)^2 - (P_0)^2/PO\}) \quad (20)$$

Where: P_i = inlet pressure; P_0 = outlet pressure; L = the length of tube; η = viscosity; R = radius of a vessel (or hydraulic radius of a noncircular vessel); V = the volume of the fluid at outlet pressure; v = the velocity of the fluid at outlet pressure. This is usually a good approximation when the flow velocity is less than Mach number 0.3. The equation has a correction factor = $((P_i + P_0)/2)/(PO)$ = ratio of the average pressure to the outlet pressure.

7.4.4.3 ELECTRICAL CIRCUIT ANALOGY

Electrical waves are analogous to the fluid. This analogy is also used to study the frequency response of fluid mechanical networks using circuit tools, where the fluid network is termed a hydraulic circuit. Poiseuille's law is analogous to the Ohm's law for electrical circuits (V = I*R, where: V = voltage, I = current and R = electrical resistance). The pressure drop (ΔP) is analogous to the voltage (V); volumetric flow rate (Q or Φ is analogous to the current (I). Then the hydraulic resistance is:

$$R = (8\eta*\Delta x)/(\pi r^4) \quad (21)$$

This concept is useful because the effective resistance in a tube is inversely proportional to the fourth power of the radius. This means that halving the radius of the tube increases the resistance to fluid movement by a factor of 16. Both Ohm's law and Poiseuille's law illustrate transport phenomena in biofluid dynamics.

7.4.4.4 LAMINAR FLOW BETWEEN TWO PARALLEL PLATES

First of all, let us consider a two-dimensional (plane) incompressible steady-state flow of viscous fluid (water) between two parallel stationary plates spaced at a distance of 2h = 0.001 m (Figs. 6 and 7). At the channel inlet, the water has standard ambient temperature (293.2 K) and a uniform inlet velocity profile of 0.1 m/s (entrance disturbances are neglected). The inlet pressure is not known beforehand, since it will be obtained from the calculation in accordance with the specified channel exit pressure of one atmosphere and the 0.023 m channel length (The fluid passes through the channel due to the pressure gradient).

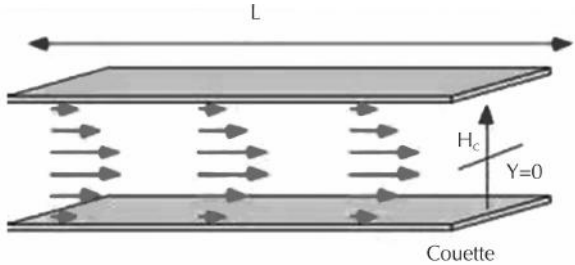
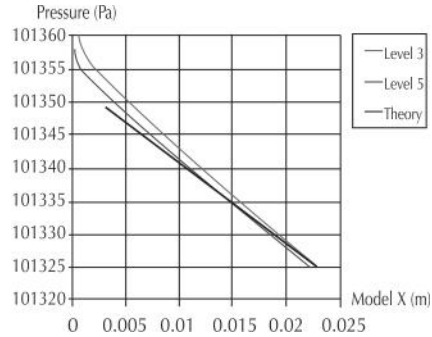


FIGURE 6 Flow between two parallel plates (9).

FIGURE 7 The solid works model for calculation 2D flow between two parallel plates (9).



FGURE 8 The longitudinal pressure change along the channel (9).

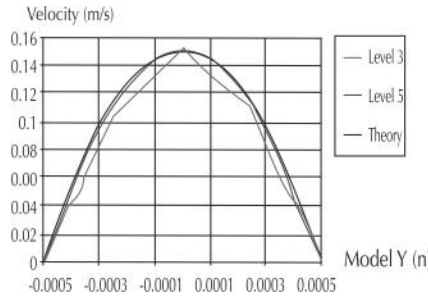


FIGURE 9 The fluid velocity profile at the channel exit (9).

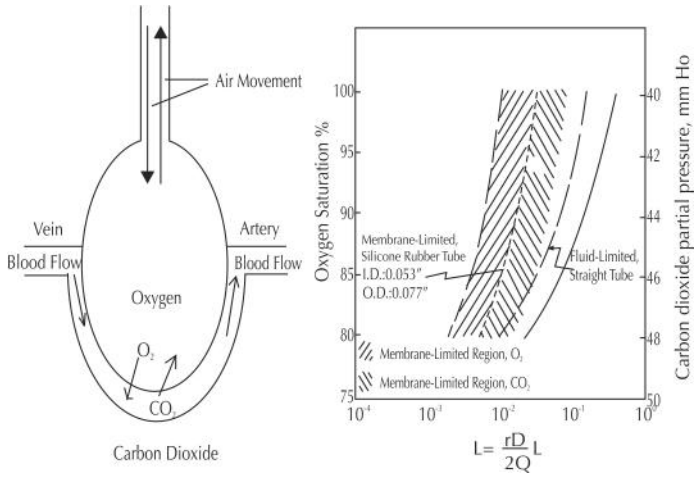


FIGURE 10 **Left:** Gas exchange at the alveolar level (16, 24, 27). **Right**: Oxygen saturation and carbon dioxide partial pressure (PCO_2) in an auxiliary lung consisting of gas-permeable tubes of circular section. The abscissa is a dimensionless length. For the fluid-limited case, the flow is assumed to be laminar and parallel to the tube axis (28).

$$u\,(y) = ((-1)/(2\,\mu))^* \,(dP/dx)^*(h^2 - y^2) \tag{22}$$

$$(dp/dx) = (-3\,\mu)/(h^2))^*(u_{average}) \tag{23}$$

Where: μ = Fluid dynamic viscosity; h= Half height of the channel; dP/dx = the longitudinal pressure gradient along the channel that is defined by Eq. (23). The Solid Works model is shown in Fig. 7 for the 2D calculation. The boundary conditions are specified as mentioned above and the initial conditions coincide with the inlet boundary conditions. The results of the calculation are presented in Figs. 8 and 9. The oxygen saturation and carbon dioxide partial pressure (PCO_2) in an auxiliary lung consisting of gas-permeable tubes of circular section are shown in Fig. 10.

7.4.4.5 FLOW THROUGH STRAIGHT TUBES

Since the Reynolds number based on the channel height is equal to about 100, the flow is laminar. Therefore, in accordance with well-known theory, after some entrance length the flow profile, the *u (y)* becomes fully developed and invariable. After some entrance length of about 0.002 m, the pressure gradient governing the channel pressure loss becomes constant, nearly the same as predicted theoretically. It is seen that the calculations performed at result resolution levels 3 and 5 yield practically the same results. Figure 9 reveals that the fluid velocity profile at the channel exit obtained from the calculation performed at result resolution level 5 is fairly close to the theoretical one, whereas the result resolution level 3 results are not so accurate (9).

The membrane-limited process is CO_2 limited and the fluid-limited process is O_2-limited. The corresponding CO_2 curves are relatively close to each other. The fluid-limited CO_2 process is five times less efficient than the membrane-limited process. The gas transfer efficiency could be improved by inducing mixing in the fluid phase. One

way of gently mixing the blood is to induce laminar secondary circulations by coiling the tubes and thereby inducing circulation centrifugal forces.

7.4.4.6 AXIAL FLOW THROUGH SPACE BETWEEN CONCENTRIC ROUND TUBES

Blood flowing axially in the annular space between concentric cylinders will be more easily oxygenated than the same flow through a straight tube. The annular geometry provides more gas exchange surface per unit blood volume than the corresponding tube and a resulting decrease in necessary diffusion times. In a study of blood-gas exchange in an annular geometry, we assume oxygen atmospheres outside the outer tube and inside the inner tube. Figure 10 shows the changes of saturation and Pco_2 a function of the dimensionless length: (DL/gq). The results depend on the gap ratio, Rg (the ratio of diameter of the outer surface of the inner membrane to the inner surface of the outer membrane).

These results are useful in the testing of auxiliary lungs designs of sheet mateial wrapped on large porous cylinders, where case the gap ratios will usually be quite large. Improved gas transfer is thus easily achieved by inducing a technique in which the outer surface of the annulus is rotated. The outer surface rotation superimposes a shear field on the axial flow field, strong enough, the shear field causes the red cells to rotate and thereby generate local transverse convection.

7.4.5 NAVIER–STOKES EQUATIONS

In fluid dynamics, the Navier–Stokes equations are named after Claude-Louis Navier and George Gabriel Stokes, and these describe the motion of fluids in vessels. These equations are derived by applying Newton's second law to fluid motion, together with the assumption that the stress in the fluid is a sum of a diffusing viscous term (proportional to the gradient of velocity) and a pressure term. The equations describe the fluid dynamics under varing conditions. They may be used to model the weather, ocean currents, fluid flow in a pipe (Fig. 11) and air flow around a wing. The Navier–Stokes equations in their full and simplified forms help with the design of aircraft and cars, the study of blood flow, the design of power stations, the analysis of pollution, and many other cases. Coupled with Maxwell's equations, they can be used to model and study magnetohydrodynamics. The Navier–Stokes equations are also of great interest in a purely mathematical sense. Somewhat surprisingly, given their wide range of practical uses, mathematicians have not yet proven that, in three dimensions, solutions always exist (existence), or that if they do exist, then they do not contain any singularity (smoothness). These are called the Navier–Stokes existence and smoothness problems.

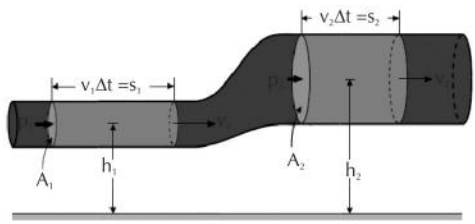


FIGURE 11 Flow through a closed round pipe: Navier–Stokes equation.

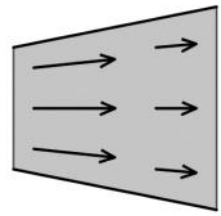


FIGURE 12 Convective acceleration in a diverging duct.

The Navier–Stokes equations dictate not position but rather velocity. A solution of the Navier–Stokes equations is called a velocity field or flow field, which is a description of the velocity of the fluid at a given point in space and time. Once the equations are solved for velocity field, other quantities of interest (such as flow rate or drag force) may be found. This is different from what one normally sees in classical mechanics, where solutions are typically trajectories of position of a particle or deflection of a continuum. Studying velocity instead of position makes more sense for a fluid. However, for visualization purposes, one can compute various trajectories (Streamlines, streak lines and path lines).

7.4.5.1 PROPERTIES OF THE NAVIER–STOKES EQUATIONS

Nonlinearity: The Navier–Stokes equations are nonlinear partial differential equations in almost every real situation. In some cases, such as one-dimensional flow and Stokes flow (or creeping flow), the equations can be simplified to linear equations. The nonlinearity makes most problems difficult or impossible to solve and is the main contributor to the turbulence that the equations model. The nonlinearity is due to convective acceleration, which is an acceleration associated with the change in velocity over position. Hence, any convective flow, whether turbulent or not, will involve nonlinearity. An example of convective but laminar (nonturbulent) flow is the passage of a viscous fluid (e.g., blood) through a small vessel. Such flows, whether exactly solvable or not, can often be thoroughly studied and understood.

Turbulence: Turbulence is the time dependent chaotic behavior seen in many fluid flows for Reynold's number >2100. It is generally thought that it is due to the inertia of the fluid as a whole: the culmination of time dependent and convective acceleration. Therefore, flows where inertial effects are small tend to be laminar. the Navier–Stokes equations describe turbulence properly.

The numerical solution of the Navier–Stokes equations for turbulent flow is extremely difficult, and due to the significantly different mixing-length scales, the stable solution of this requires such a fine mesh resolution that the computational time becomes significantly infeasible for calculation. Attempts to solve turbulent flow using a laminar solver typically result in a time-unsteady solution, which fails to converge appropriately. To counter this, time-averaged equations such as the Reynolds-averaged Navier–Stokes equations (RANS), supplemented with turbulence models, are used in practical computational fluid dynamics (CFD) applications. Some models include the Spalart-Allmaras, k-ω (k-omega), k-ε (k-epsilon), and SST turbulence models which add a variety of additional equations to bring closure to the RANS equations.

Another technique for solving the Navier–Stokes equation is the **Large Eddy Simulation** (LES). This approach is computationally more expensive than the RANS method (in time and computer memory), but produces better results since the larger turbulent scales are explicitly resolved.

Applicability: Together with supplemental equations (e.g., law of conservation of mass) and well-formulated boundary conditions, the Navier–Stokes equations can model fluid motion accurately. Even the turbulent flows seem (on average) to agree with real world observations.

The Navier–Stokes equations assume: The fluid is a continuum (The continuity equation is applicable); fluid is not moving at relativistic velocities; under extreme conditions. Actually, real fluids will produce results different from the continuous fluids modeled by the Navier–Stokes equations. Depending on the Knudsen number of the problem, statistical mechanics or possibly even molecular dynamics may be a more appropriate approach. Another limitation is a complicated nature of these equations. Time tested formulations exist for common fluid families, but the application of the Navier–Stokes equations to less common families tends to result in very complicated formulations which are an area of current research. For this reason, these equations are usually written for Newtonian fluids. Studying Newtonian fluids is "simple" because the viscosity model ends up being linear. However, general models for the nonnewtonian fluids (such as blood) do not exist.

7.4.5.2 GENERALIZED NAVIER–STOKES EQUATIONS

The derivation of the Navier–Stokes equations begins with an application of Newton's second law (Law of conservation of momentum), law of conservation of mass, and law of conservation of energy for an arbitrary portion of the fluid. In an inertial frame of reference, the general form of the Navier–Stokes equations is:

$$\rho\left(\frac{\partial v}{\partial t} + v.\nabla v\right) = -\nabla p + \nabla.T + f \tag{24}$$

Where: v is the flow velocity; ρ is the fluid density; p is the pressure; T is the (deviatoric) component of the total stress tensor; f represents body forces (per unit volume) acting on the fluid; ∇ is the del operator; **∇p =** is called the pressure gradient due to the isotropic part of the Cauchy stress tensor; and **∇.T is the** anisotropic part of the stress tensor that conventionally describes viscous forces for incompressible flow. The Eq. (24) is a law conservation of momentum in a continuous fluid. This equation is also applicable to any nonrelativistic continuum and is known as the Cauchy momentum equation. The Eq. (24) is often written using the material derivative (Dv/Dt):

$$\rho\left(\frac{Dv}{Dt}\right) = -\nabla p + \nabla.T + f \tag{25}$$

The left side of the Eq. (25) describes the acceleration, and may be composed of time dependent or convective effects (also the effects of noninertial coordinates if present). The right side of the equation is in effect a summation of body forces (such as gravity) and divergence of stress (pressure and shear stress). An example of convection (Fig. 12): Though the flow may be steady (time independent), the fluid decelerates as it

moves down the diverging duct (assuming incompressible or subsonic compressible flow), hence there is an acceleration happening over position. A significant feature of the Navier–Stokes equations is the presence of convective acceleration: the effect of time independent acceleration of a fluid with respect to space. While individual fluid particles are indeed experiencing time dependent acceleration, the convective acceleration of the flow field is a spatial effect, one example being fluid speeding up in a nozzle. Convective acceleration is represented by the nonlinear quantity: **(v. ∇v),** where: **∇v** is the tensor derivative of the velocity vector, equal in Cartesian coordinates to the component-by-component gradient. The convection term may, by a vector calculus identity, be expressed without a tensor derivative:

$$\mathbf{(v.\ \nabla v) = \nabla\ ((||v||)^2/2) + (\nabla\ x\ v)\ x\ v} \tag{26}$$

The Eq. (26) has an irrotational flow, where the curl of the velocity (called vorticity: $\omega = \nabla\ x\ \mathbf{v}$) is equal to zero. Regardless of what kind of fluid is being dealt with, convective acceleration is a nonlinear effect. Convective acceleration is present in most flows (exceptions include one-dimensional incompressible flow), but its dynamic effect is disregarded in Stokes flow. The Navier–Stokes equations is based on the following assumptions on the deviatoric stress tensor (**T**):

- The deviatoric stress vanishes for a fluid at rest; and does not depend directly on the flow velocity itself, but only on spatial derivatives of the flow velocity

In the Navier–Stokes equations, the deviatoric stress is expressed as the product of the tensor gradient (∇v) of the flow velocity with a viscosity tensor A, i.e.: T = A (∇v).

- The fluid is assumed to be isotropic, as valid for gases and simple liquids, and consequently A is an isotropic tensor; furthermore, since the deviatoric stress tensor is symmetric, it turns out that it can be expressed in terms of two scalar dynamic viscosities μ and μ": Δ = **∇.v**. The rate of expansion of the flow the deviatoric stress tensor has zero trace, so for a three-dimensional flow: $2\mu + 3\mu" = 0$.

As a result, in the Navier–Stokes equations, the deviatoric stress tensor has the following form for rate of strain tensor (**E**) and the dynamic viscosity (μ):

$$\mathbf{T = 2\ \mu\ (E - 0.33\ \Delta I)} \tag{27}$$

7.4.6 DARCY'S LAW

Darcy's law describes the flow of a fluid through a porous medium. The law was formulated by Henry Darcy based on the results of experiments on the flow of water through beds of sand. It also forms the scientific basis of fluid permeability used in the earth sciences, particularly in hydrogeology. Although Darcy's law (an expression of Law of Conservation of Momentum) was determined experimentally by Darcy, yet it can be derived from the Navier-Stokes equations. It is analogous to Fourier's law in the field of heat conduction, Ohm's law in the field of electrical networks, or Fick's law in the diffusion process. The combination of Darcy's law and the conservation of mass equation is equivalent to the groundwater flow equation. Darcy's law can also describe the fluid flows in specific organs of biological species. Darcy's law is a relationship between the instantaneous discharge rate through a porous medium, the viscosity of the fluid and the pressure drop over a given distance:

$$Q = ((-kA)/\mu) * ((P_b - P_a)/L) \quad (28)$$

The total discharge (Q: Volume per time, m^3/s) is equal to the product of the permeability of the medium (k, m^2), the cross-sectional area to flow (A, m^2), the pressure drop per unit length (= $(P_b - P_a)/L$), and all divided by the viscosity (μ, Pa·s). The negative sign is needed because fluid flows from high pressure to low pressure. If the change in pressure is negative (where $P_a > P_b$), then the flow will be in the positive 'x' direction. Dividing both sides of the equation by the area, we have the equation for the flux (q: discharge per unit area, m/s):

$$q = (—k/\mu)*\nabla P \quad (29)$$

Where: q is the Darcy flux; ∇P is the pressure gradient vector (Pa/m). The pore velocity (v) is related to the Darcy flux (q) by the porosity (n). The flux is divided by porosity to account for the fact that only a fraction of the total formation volume is available for flow (v = q/n). Darcy's law is a simple mathematical statement, which neatly summarizes several familiar properties:

- If there is no pressure gradient over a distance, no flow occurs (these are hydrostatic conditions);
- If there is a pressure gradient, flow will occur from high pressure towards low pressure (opposite the direction of increasing gradient—hence the negative sign in Darcy's law);
- The greater the pressure gradient (through the same formation material), the greater the discharge rate; and
- The discharge rate of fluid will often be different—through different formation materials (or even through the same material, in a different direction)—even if the same pressure gradient exists in both cases.

Darcy's law is only valid for slow and viscous flow. Typically Darcy's law is applicable for any flow with a Reynolds number less than one. Experimental tests have shown that flow regimes with Reynolds numbers up to 10 may still be Darcian. For very short time scales, a time derivative of flux may be added to Darcy's law, which results in valid solutions at very small times (in heat transfer, this is called the modified form of Fourier's law):

$$((\tau)(dq/dt) + q) = -K*\nabla h \quad (30)$$

Where: τ is a very small time constant which causes the equation to reduce to the normal form of Darcy's law at «normal» times (> nanoseconds). This form is more mathematically rigorous, but leads to a hyperbolic flow equation, which is more difficult to solve and is only useful at very small times, typically out of the realm of practical use. Darcy's law is valid only for flow in continuum region. For a flow in transition region, where both viscous and Knudsen friction are present, following binary friction model is used:

$$\nabla P = -q^* ((k/\mu) + D_K)^{-1} \quad (31)$$

Where: D_K is the Knudsen diffusivity of the fluid in porous media. A darcy (or darcy unit) and millidarcy (mD) are units of permeability, named after Henry Darcy. They

are not SI units. Like other measures of permeability, a darcy has the same units as area. A medium with a permeability of one darcy permits a flow of 1 cm^3/s of a fluid with viscosity one cP (1 mPa·s) under a pressure gradient of one atm/cm acting across an area of one cm^2. A millidarcy (mD) is equal to 0.001 darcy and a microdarcy (μD) equals 0.000001 darcy. Water has a viscosity of 1.0019 cP at about room temperature. Converted to SI units, one darcy is equivalent to 9.869233×10^{-13} m^2 or 0.9869233 $(\mu m)^2$. This conversion is usually approximated as one $(\mu m)^2$ = the reciprocal of 1.013250. Permeability measures the ability of fluids to flow through porous media).

7.4.7 THE LAW OF LAPLACE

Francis Hauksbee performed some of the earliest observations and experiments in 1709 and these were repeated in 1718 by James Jurin who observed that the height of fluid in a capillary column was a function only of the cross-sectional area at the surface, not of any other dimensions of the column. In 1804, Thomas Young laid the foundations of the equation in his 1804 paper, "*An Essay on the Cohesion of Fluids*." In this classical paper, he set out in descriptive terms the principles governing contact between fluids (along with many other aspects of fluid behavior). Pierre Simon Laplace followed this up in Mécanique Céleste with the formal mathematical description that reproduced in symbolic terms the relationship described earlier by Young. Laplace accepted the idea propounded by Hauksbee in his book *Physico – Mechanical Experiments* (1709): the phenomenon was due to a force of attraction that was insensible at sensible distances. The part which deals with the action of a solid on a liquid and the mutual action of two liquids was not worked out thoroughly, but ultimately was completed by Gauss. Carl Neumann later filled in a few details.

In physics, the Young–Laplace equation is a nonlinear partial differential equation that describes the capillary pressure difference sustained across the interface between two static fluids, such as water and air, due to the phenomenon of surface tension or wall tension, although usage on the latter is only applicable if assuming that the wall is very thin. The Young–Laplace equation relates the pressure difference to the shape of the surface or wall and it is fundamentally important in the study of static capillary surfaces. Young–Laplace equation is a statement of normal stress balance for static fluids meeting at an interface, where the interface is treated as a surface (zero thickness):

$$\Delta p = \left(-\gamma * \{\nabla \cdot \tilde{n}\} = \gamma * \left(1/R1\right) + \left(1/R2\right)\right) = \left(2 * \gamma * H\right) \tag{32}$$

Where: Δp = the pressure difference across the fluid interface; γ = the surface tension (or wall tension); ñ = the unit normal pointing out of the surface; H = the mean curvature = (1/R); and R_1 and R_2 = the principal radii of curvature. Several bioengineers refer inappropriately to the factor "2*H" as the total curvature. Also for very small thickness of a vessel, R1 is almost equal to R2. Therefore we have::

$$((1/R1) + (1/R2)) = ((R1 + R2)/(R1*R2)) = (2R/R^2) = (2/R) = 2*H \tag{33}$$

Note that only normal stress is considered, this is because it can be shown that a static interface is possible only in the absence of tangential stress.

7.4.7.1 CAPILLARY PRESSURE IN A TUBE

In a sufficiently narrow (i.e., low Bond number) tube of circular cross-section (radius a), the interface between two fluids forms a meniscus that is a portion of the surface of a sphere with radius R. The pressure drop across this surface is:

$$\Delta p = ((2*\gamma)/R) \tag{34}$$

This may be shown by writing the Young–Laplace equation in spherical form with a contact angle boundary condition and also a prescribed height boundary condition at, say, the bottom of the meniscus. The solution is a portion of a sphere, and the solution will exist only for the pressure difference shown above. This is significant because there is not another equation or law to specify the pressure difference; existence of solution for one specific value of the pressure difference prescribes it. The radius of the sphere is a function only of the contact angle, θ, which in turn depends on the exact properties of the fluids and the solids in which they are in contact:

$$R = (a/\cos\theta) \tag{35}$$

Combining Eqs. (2) and (3), we get:

$$\Delta p = ((2*\gamma*\cos\theta)/a)$$

In order to maintain hydrostatic equilibrium, the induced capillary pressure is balanced by a change in height, hr, which can be positive or negative, depending on whether the wetting angle is less than or greater than 90° (See Figs. 13 and 14). For a fluid of density ρ and for $\Delta p = h*\rho g$:

$$h = ((2*\gamma*\cos\theta)/(\rho g\, a)) \tag{36a}$$

Where: g is the acceleration due to gravity = 9.81 m/s^2. This is sometimes known as the Jurin rule or Jurin height after James Jurin who studied the effect in 1718. For a water-filled glass tube in air at sea level with the following data, the height of the water column (H, meters) is given by:

γ = 0.0728 J/m^2 at 20°C	θ = 20° (0.35 rad)
ρ = 1000 kg/m3	g = 9.81 m/s^2

$$H = ((1.4 \times 10^{-5})/a), \text{ meters} \tag{36b}$$

Thus for a 2 mm wide (1 mm radius) tube, the water would rise 14 mm. However, for a capillary tube with radius 0.1 mm, the water would rise 14 cm (about 6 inches). In the general case, for a free surface and where there is an applied "overpressure," Δp, at the interface in equilibrium, there is a balance between the applied pressure, the hydrostatic pressure and the effects of surface tension. The Young–Laplace equation becomes:

$$\Delta p = \{(h*\rho g) - \gamma*((1/R1) + (1/R2))\} \tag{37}$$

The equation can be nondimensionalized in terms of its characteristic length-scale, the capillary length and the characteristic pressure:

$$L_c = (\gamma/(\gamma))^{0.5} \text{ and}$$

$$P_c = (\gamma/L_c) = (\gamma^* \rho g)^{0.5} \quad (38)$$

For clean water at standard temperature and pressure, the capillary length is ~2 mm. The nondimensional equation then becomes:

$$(h^* - \Delta p) = ((1/R1^*) + (1/R2^*)) \quad (39)$$

Thus, the surface shape is determined by only one parameter, the over pressure of the fluid, Δp^* and the scale of the surface is given by the capillary length. The solution of the equation requires an initial condition for position, and the gradient of the surface at the start point.

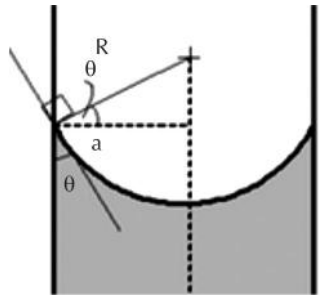
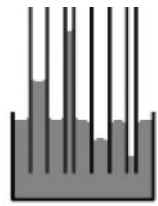


FIGURE 13 Spherical meniscus with wetting angle less than 90°.



Left two capillaries = contact angle less than 90°;
Right two capillaries = contact angle greater than 90°.

FIGURE 14 Liquid rise in a capillary tube.

7.4.7.2 APPLICATION OF "LAPLACE LAW" IN BIOENGINEERING

In medicine, it is often referred to as the Law of Laplace, used in the context of cardiovascular physiology, and also respiratory physiology. Arteries may be viewed as cylinders, and the left ventricle of the heart can be viewed as part cylinder, part hemisphere (a bullet shape), modeled by the Law of Laplace as: (T = (p x r)/(2 x t)), where: T = wall tension, p = pressure, r = radius, t = wall thickness. For a given pressure, increased radius requires increased wall thickness to accommodate a stable wall tension. Also, increased pressure requires increased thickness to maintain a stable wall tension. The latter is used to explain thickening of arteries and thickening of the left ventricle to accommodate high blood pressure. However, the thickened left ventricle is stiffer

than when the thickness is normal, so it requires elevated pressures to fill, a condition known as diastolic heart failure.

The lung contains small spherical gas-exchange chambers called alveoli, where a single alveolus can be modeled as being a perfect sphere. The Law of Laplace explains why alveoli of the lung need small radii to accommodate their thin walls for gas exchange at atmospheric pressure. The presence of numerous alveoli with small radii also results in high surface area, which is advantageous for gas exchange.

Applying the Law of Laplace to alveoli of the lung, the pressure differential results in an external force that pushes on the surface of the alveolus, tending to decrease size during exhalation. The Law of Laplace states that pressure is inversely proportional to alveolar radius, and directly proportional to surface tension. It follows from this that if the surface tensions are equal, a small alveolus will experience a greater inward pressure than a large alveolus. In that case, if both alveoli are connected to the same airway, the small alveolus will be more likely to collapse, expelling its contents into the large alveolus.

This explains why the presence of surfactant lining the alveoli is of vital importance. Surfactant lining reduces the surface tension on all alveoli, but its effect is greater on small alveoli than on large alveoli. Thus, surfactant compensates for the size differences between alveoli, and ensures that smaller alveoli do not collapse. One can mimic this effect by connecting two inflated balloons to either ends of a plastic straw or a stiffer tube. If the balloons are equal in thickness and radius then they can stay equally inflated, but if one squeezes one a bit to reduce its radius, the condition will be unstable, and in accord with the Law of Laplace, the smaller one will empty itself into the larger one.

The Law of Laplace also explains various phenomena encountered in the pathology of vascular or gastrointestinal walls. The wall tension in this case represents the muscular tension on the wall of the vessel. For example, if an aneurysm forms in a blood vessel wall, the radius of the vessel has increased. This means that the inward force on the vessel decreases, and therefore the aneurysm will continue to expand until it ruptures. A similar logic applies to the formation of diverticuli in the gut.

The Law of Laplace can also be used to model transmural pressure in the heart and the rest of the circulatory system.

7.4.8 VENTILATION/PERFUSION RATIO

In respiratory physiology, the ventilation/perfusion ratio (or V/Q ratio) is a ratio of the amount of air reaching the alveoli (V, ventilation) to the amount of blood reaching the alveoli (Q, perfusion). These two variables constitute the main determinants of the blood oxygen concentration. The V/Q ratio can be measured with a ventilation/perfusion scan.

Ideally, the oxygen provided via ventilation is just enough to saturate the blood fully. In the typical adult, one liter of blood can hold about 200 mL of oxygen; one liter of dry air has about 210 mL of oxygen. Therefore, under these conditions, the ideal ventilation-perfusion ratio would be about 1.05. If one were to consider humidified air (with less oxygen), then the ideal V/Q ratio is in the vicinity of 1.0, thus leading to concept of ventilation-perfusion equality or ventilation-perfusion matching. This

matching may be assessed in the lung as a whole, or in individual or in subgroups of gas-exchanging units in the lung. On the other side, ventilation-perfusion mismatch is a term used when the ventilation and the perfusion of a gas exchanging unit are not matched. The actual values in the lung vary depending on the position within the lung. If taken as a whole, the typical value is approximately 0.8. Because the lung is centered vertically around the heart, part of the lung is superior to the heart, and part is inferior. This has a major impact on the V/Q ratio: apex of lung – higher; and base of lung – lower.

In a subject standing in orthostatic position (upright), the apex of the lung shows higher V/Q ratio, while at the base of the lung the ratio is lower but nearer to the optimal value for reaching adequate blood oxygen concentrations. The main reason for lower V/Q ratios at the base is that both ventilation and perfusion increase when going from the apex to the base, but Q does it more strongly thus lowering the V/Q ratio. The principal factor involved in the genesis of V/Q dishomogeneity between the apex and the base of the lung is gravity. This is why V/Q ratios change in positions other than the orthostatic one.

7.4.8.1 VENTILATION

Gravity and weight of the lung act on ventilation by increasing pleural pressure at the base (making it less negative) and thus reducing the alveolar volume. The lowest part of the lung in relation to gravity is called the dependent region. At the dependent region smaller volumes mean the alveoli are more compliant (more distensible) and so capable of wider oxygen exchanges with the external environment. The apex, though showing a higher oxygen partial pressure, ventilates less efficiently since its compliance is lower and so smaller volumes are exchanged.

7.4.8.2 PERFUSION

The impact of gravity on pulmonary perfusion expresses itself as the hydrostatic pressure of the blood passing through the branches of the pulmonary artery in order to reach the apical and basal district of the lung, acting respectively against or synergistically with the pressure developed by the right ventricle. Thus at the apex of the lung the resulting pressure can be insufficient for developing a flow (which can be sustained only by the negative pressure generated by venous flow towards the left atrium) or even for preventing the collapse of the vascular structures surrounding the alveoli, while the base of the lung shows an intense flow due to the higher resulting pressure.

An area with no ventilation (and thus a V/Q ratio = zero) is termed «shunt." An area with no perfusion (and thus a V/Q undefined though approaching infinity) is termed dead space. A lower V/Q ratio (with respect to the expected value for a particular lung area in a defined position) impairs pulmonary gas exchange and is a cause of low arterial partial pressure of oxygen (p_aO_2). Excretion of carbon dioxide is also impaired, but a rise in the arterial partial pressure of carbon dioxide (p_aCO_2) is very uncommon because this leads to respiratory stimulation and the resultant increase in alveolar ventilation returns p_aCO_2 to within the normal range. These abnormal phenomena are usually seen in chronic bronchitis, asthma, hepatopulmonary syndrome, and acute pulmonary edema. A high V/Q ratio increases p_aO_2 and decreases $paCO_2$. This finding is typically associated with pulmonary embolism (where blood circulation is

impaired by an embolus). Ventilation is wasted, as it fails to oxygenate any blood. A high V/Q can also be observed in COPD as a maladaptive ventilatory overwork of the undamaged lung parenchyma.

7.4.9 MAXIMAL VOLUME OF OXYGEN CONSUMPTION ($VO_{2\ MAX}$)

$VO_{2\ max}$ (also known as: maximal oxygen consumption, maximal oxygen uptake, peak oxygen uptake or maximal aerobic capacity) is the maximum capacity of a human body to transport and use oxygen during incremental exercise, which reflects the physical fitness of an individual. $VO_{2\ max}$ is expressed either as an absolute rate in liters of oxygen per minute (L/min) or as a relative rate in milliliters of oxygen per kilogram of bodyweight per minute (ml/kg/min). The latter expression is often used to compare the performance of endurance sports athletes.

7.4.9.1 MEASURING $VO_{2\ MAX}$

Accurately measuring $VO_{2\ max}$ involves a physical effort sufficient in duration and intensity to fully tax the aerobic energy system. In general clinical and athletic testing, this usually involves a graded exercise test (either on a treadmill or on a cycle ergometer, Fig. 15) in which exercise intensity is progressively increased while measuring ventilation, oxygen and carbon dioxide concentration of the inhaled and exhaled air. $VO_{2\ max}$ is reached when oxygen consumption remains at steady state despite an increase in workload. $VO_{2\ max}$ is properly defined by the Fick's equation:

$$VO_{2\ max} = (Q * (CaO_2 - CvO_2) \tag{40}$$

Where: Q is the cardiac output of the heart, CaO_2 is the arterial oxygen content, CvO_2 is the venous oxygen content, and $(CaO_2 - CvO_2)$ is also known as the arteriovenous oxygen difference. These values in Fick's equation are obtained during an exertion at a maximal effort.

FIGURE 15 $VO_{2\ max}$ measurement through a modern metabolic cart during a graded exercise test on a treadmill (Stress test).

7.4.9.2 ESTIMATION OF $VO_{2\ MAX}$

Tests measuring $VO_{2\ max}$ can be dangerous in individuals who are not considered normal healthy subjects, as any adverse condition with the respiratory and cardiovascular

systems will be greatly exacerbated in clinically ill patients. Thus, many protocols for estimating $VO_{2\,max}$ have been developed for those for high risk patients. These generally are similar to a $VO_{2\,max}$ test, but do not reach the maximum of the respiratory and cardiovascular systems and are called submaximal tests.

Another estimate of $VO_{2\,max}$, based on maximum and resting heart rates, was created by a group of researchers from Denmark: Uth–Sørensen–Overgaard–Pedersen**. Denmark estimation of $VO_{2\,max}$** is shown below:

$$VO_{2\,max} = (15^* \{HR_{max}/HR_{rest}\}) \tag{41}$$

This equation uses maximum heart rate (HR_{max}) and resting heart rate (HR_{rest}) to estimate $VO_{2\,max}$ in mL/min/kg.

7.4.9.3 COOPER TEST FOR ESTIMATION OF $VO_{2\,MAX}$

Kenneth H. Cooper conducted a study for the United States Air Force in the late 1960s. The Cooper test is based on the distance covered in 12 min during running. Based on the measured distance, an estimate of $VO_{2\,max}$ (in mL/min/kg) is given below:

$$VO_{2\,max} = (\{d_{12}\_505\}/\{45\}) \tag{42}$$

Where: d_{12} is distance (in meters) covered in 12 min. There are several other reliable tests and $VO_{2\,max}$ calculators to estimate $VO_{2\,max}$, most notably the multistage fitness test (or bleep test). The bleep test is based on the research paper by "Leger and Lambert, A Maximal Multi-Stage 20 m Shuttle Run Test to predict $VO_{2\,max}$."

7.4.9.4 $VO_{2\,MAX}$ LEVELS

Maximal oxygen uptake ($VO_{2\,max}$) is widely accepted as the single best measure of cardiovascular fitness and maximal aerobic power. Absolute values of $VO_{2\,max}$ are typically 40 to 60% higher in men than in women. The average untrained healthy male will have a $VO_{2\,max}$ of approximately 35–40 mL/kg/min. The average untrained healthy female will score a $VO_{2\,max}$ of approximately 27–31 mL/kg/min. These scores can improve with training and decrease with age, though the degree of trainability also varies very widely: conditioning may double $VO_{2\,max}$ in some individuals, and will marginally improve it in others.

In sports where endurance is an important component in performance, such as cycling/rowing/cross-country skiing/swimming/running, world class athletes typically will have a high $VO_{2\,max}$. Elite male runners can consume up to 85 mL/kg/min, and female elite runners can consume about 77 mL/kg/min. "Five time Tour de France winner Miguel Indurain" is reported to have had a $VO_{2\,max}$ of 88.0 at his peak, while cross-country skier Bjørn Dæhlie measured at 96 mL/kg/min. Norwegian cyclist Oskar Svendsen at an age 18 years is thought to have recorded the highest $VO_{2\,max}$ of 97.5 mL/kg/min. To put this into perspective, thoroughbred horses have a $VO_{2\,max}$ of around 180 mL/kg/min. "Siberian dogs running in the Iditarod Trail Sled Dog Race" have $VO_{2\,max}$ values as high as 240 mL/kg/min. The highest values in absolute terms are often found in rowers, as their much greater bulk makes up for a slightly lower $VO_{2\,max}$ per kg. Elite oarsman measured in 1984 had $VO_{2\,max}$ values of 6.1 L/min and oarswoman 4.1 L/min. Rowers are interested in both absolute values of $VO_{2\,max}$ and in lung capacity, and the fact that they are measured in similar units means that the two

are often confused. British rower Sir Matthew Pinsent is reported to have had a $VO_{2\ max}$ of 7.5l/min. New Zealand sculler Rob Waddell has one of the highest absolute $VO_{2\ max}$ levels ever tested.

7.4.9.5 FACTORS AFFECTING $VO_{2\ MAX}$

The factors affecting $VO_{2\ max}$ are often divided into supply and demand factors. Supply is the transport of oxygen from the lungs to the mitochondria (including lung diffusion, stroke volume, blood volume, and capillary density of the skeletal muscle) while demand is the rate at which the mitochondria can reduce oxygen in the process of oxidative phosphorylation. Of these, the supply factor is often considered to be the limiting one. However, it has also been argued that while trained subjects probably are supply limited, untrained subjects can indeed have a demand limitation. Tim Noakes, a professor of exercise and sports science at the University of Cape Town, describes a number of variables that may affect $VO_{2\ max}$: age, gender, fitness and training, changes in altitude, and action of the ventilatory muscles. Noakes also asserts that $VO_{2\ max}$ is a relatively poor predictor of performance in runners due to variations in running economy and fatigue resistance during prolonged exercise.

Cardiac output, pulmonary diffusion capacity, oxygen carrying capacity, and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of $VO_{2\ max}$ determinants. The body works as a system. If one of these factors is subpar, then the whole system loses its normal capacity to function properly. In theory, the drug Erythropoietin (EPO) can boost $VO_{2\ max}$ by a significant amount. This makes it attractive to athletes in endurance sports like professional cycling. By 1998 it had become widespread in cycling and led to the Festina affair as well as being mentioned ubiquitously in the USADA 2012 report on the US Postal team. Greg LeMond has suggested establishing a baseline for riders' $VO_{2\ max}$ (and other attributes) to detect abnormal performance increases.

7.4.10 CHLORIDE SHIFT

It is also known as the "Hamburger shift or Hamburger's phenomenon," named after Hartog Jakob Hamburger. The Chloride effect is a process which occurs in a cardiovascular system and refers to the exchange of bicarbonate (HCO^{3-}) and chloride (Cl-) ions across the membrane of red blood cells (RBCs).

7.4.10.1 MECHANISM

Carbon dioxide (CO_2) generated in tissues passively diffuses into capillaries via the interstitial fluid. Once in circulation, CO_2 enters red blood cells (RBCs) to balance the intracellular and extracellular CO_2 concentrations. RBCs contain appreciable quantities of carbonic anhydrase, an enzyme which converts CO_2 to carbonic acid and which is not highly expressed in interstitial fluid and plasma. RBC carbonic anhydrase converts dissolved CO_2 and intracellular water to carbonic acid (H_2CO_3), which spontaneously dissociates to form bicarbonate (HCO^{-3}) and a hydrogen ion (H^+). In response to the fall of intracellular CO_2, more CO_2 passively diffuses into the cell. RBCs are impermeable to hydrogen ions but are able to exchange bicarbonate ions for chloride ions across Band 3. The chloride intake and bicarbonate export are due to rise in intracellular bicarbonate. The term "chloride shift" refers to this exchange. As a

result, blood chloride concentration is lower in systemic venous blood than in systemic arterial blood or in pulmonary circulation. The opposite process occurs when blood O_2 concentrations rise and the Haldane effect occurs. Release of hydrogen ions from hemoglobin increases H^+ concentration within RBCs, shifting the equilibrium towards CO_2, and water formation from bicarbonate. The subsequent decrease in intracellular bicarbonate concentration reverses chloride-bicarbonate exchange. Inward movement of bicarbonate across Band 3 allows carbonic anhydrase to convert it to CO_2 for expiration. The chloride shift may also regulate the affinity of hemoglobin for oxygen through the chloride ion acting as an allosteric effector. Following reactions occur in the lungs:

Bicarbonate in the red blood cell (RBC) exchange with chloride from plasma.			(43)
PLASMA		**RBC**	
HCO^3	$— \rightarrow \rightarrow \rightarrow$	HCO^{3-}	
Na^+		K^+	
Cl-	$\leftarrow\leftarrow\leftarrow\leftarrow$	Cl-	

The underlying properties creating the chloride shift are the presence of carbonic anhydrase within the RBC but not the blood, and the permeability of the blood to bicarbonate but not to hydrogen. Exchange of bicarbonate for chloride ions across the erythrocyte cell membrane maintains the electrical neutrality of the cell. Bicarbonate moves against its concentration gradient: erythrocyte (HCO^3) is about 15 mmol/L; plasma (HCO^3) is about 24 mmol/L. Chloride moves down its concentration gradient. This active transport is facilitated by the Band 3 anion exchanger protein.

7.4.11 BOHR EFFECT

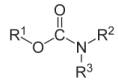
The Bohr Effect is a physiological phenomenon first described in 1904 by the Danish physiologist Christian Bohr (father of physicist Niels Bohr and so grandfather of physicist Aage Bohr). It states that hemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide. This implies that a decrease in blood pH or an increase in blood CO_2 concentration will result in hemoglobin proteins releasing the loads of oxygen, and a decrease in carbon dioxide or increase in pH will result in hemoglobin picking up more oxygen. Since carbon dioxide reacts with water to form carbonic acid, an increase in CO_2 results in a decrease in blood pH.

7.4.11.1 MECHANISM

In deoxyhemoglobin, the N-terminal amino groups of the α-subunits and the C-terminal histidine of the β-subunits participate in ion pairs. The formation of ion pairs causes them to decrease in acidity. Thus, deoxyhemoglobin binds one proton (H^+) for every two O_2 released. In oxyhemoglobin, these ion pairings are absent and these groups increase in acidity. Consequentially, a proton is released for every two O_2 bound. Specifically, this reciprocal coupling of protons and oxygen is the Bohr effect.

Additionally, carbon dioxide reacts with the N-terminal amino groups of α-subunits to form carbamates:

$$R - NH_2 + CO_2 \longleftrightarrow R - NH - COO^- + H^+ \quad (44)$$



Carbamate is derived from carbamic acid.

Deoxyhemoglobin binds to CO_2 more readily to form a carbamate than oxyhemoglobin. Carbamates are organic compounds derived from carbamic acid (NH_2COOH). When CO_2 concentration is high (as in the capillaries), the protons released by carbamate formation further promotes oxygen release. Although the difference in CO_2 binding between the oxy and deoxy states of hemoglobin accounts for only 5% of the total blood CO_2, it is responsible for half of the CO_2 transported by blood. This is because 10% of the total blood CO_2 is lost through the lungs in each circulatory cycle.

7.4.11.2 PHYSIOLOGICAL ROLE

The Bohr Effect facilitates oxygen transport as hemoglobin binds to oxygen in the lungs, but then releases it in the tissues, particularly those tissues in most need of oxygen. When a tissue's metabolic rate increases, its carbon dioxide production increases. Carbon dioxide forms bicarbonate through the following reaction:

$$H_2O + CO_2 \longleftrightarrow H^+ + HCO^{3-} \quad (45)$$

Although the reaction usually proceeds very slowly, the enzyme family of carbonic anhydrase, which is present in red blood cells, accelerates the formation of bicarbonate and protons. This causes the pH of tissues to decrease thus promoting the dissociation of oxygen from hemoglobin to the tissue, allowing the tissue to obtain enough oxygen to meet its demands. Conversely, in the lungs, where oxygen concentration is high, binding of oxygen causes hemoglobin to release protons, which combine with bicarbonate to drive off carbon dioxide in exhalation. Since these two reactions are closely matched, there is little change in blood pH.

The dissociation curve shifts to the right when carbon dioxide or hydrogen ion concentration is increased. This facilitates increased oxygen dumping. This mechanism allows for the body to adapt the problem of supplying more oxygen to tissues. When muscles are undergoing strenuous activity, they generate CO_2 and lactic acid as products of cellular respiration and lactic acid fermentation. In fact, muscles generate lactic acid so quickly that pH of the blood passing through the muscles will drop to around 7.2. As lactic acid releases its protons, the pH decreases that causes hemoglobin to release ~10% more oxygen.

7.4.12 ROOT EFFECT

R. W. Root discovered the "Root Effect," which is a physiological phenomenon that occurs in fish hemoglobin. In the Root Effect, an increased proton or carbon dioxide concentration (lower pH) lowers hemoglobin's affinity and carrying capacity for oxygen. The Root effect is to be distinguished from the Bohr effect where only the affinity to oxygen is reduced. Hemoglobins showing the root effect show a loss

of cooperativity at low pH. This results in the Hb-O_2 dissociation curve being shifted downward and not just to the right. At low pH, hemoglobins showing the root effect do not become fully oxygenated even at oxygen tensions up to 20 kPa. This effect allows hemoglobin in fish with swim bladders to unload oxygen into the swim bladder against a high oxygen gradient. The effect is also noted in the choroid rete, the network of blood vessels which carries oxygen to the retina. In the absence of the Root effect, retia will result in the diffusion of some oxygen directly from the arterial blood to the venous blood, making such systems less effective for the concentration of oxygen.

7.4.13 HALDANE EFFECT

John Scott Haldane described "Haldane Effect." The Haldane Effect is a property of hemoglobin, where deoxygenation of the blood increases its ability to carry carbon dioxide. Conversely, oxygenated blood has a reduced capacity for carbon dioxide. The general equation for the Haldane Effect is:

$$H^+ + HbO_2 \longleftrightarrow H^+Hb + O_2 \tag{46}$$

However, this equation is confusing as it reflects primarily the Bohr Effect. The significance of this equation lies in realizing that oxygenation of Hb promotes dissociation of H^+ from Hb that shifts the bicarbonate buffer equilibrium towards CO_2 formation. Therefore, CO_2 is released from RBCs. In patients with lung disease, lungs may not be able to increase alveolar ventilation in the face of increased amounts of dissolved CO_2. This partially explains the observation that some patients with emphyzema might have an increase in partial pressure of arterial dissolved carbon dioxide ($P_{a(CO_2)}$) following administration of supplemental oxygen even if content of CO_2 stays equal.

7.4.14 ALVEOLAR GAS EQUATION

The partial pressure of oxygen (pO_2) in the pulmonary alveoli is required to calculate both the alveolar-arterial gradient of oxygen and the amount of right-to-left cardiac shunt, which are both clinically useful quantities. However it is not practical to take a sample of gas from the alveoli in order to directly measure the partial pressure of oxygen. The alveolar gas equation allows the calculation of the alveolar partial pressure of oxygen from data that is practically measurable. It was first characterized in 1946. The equation relies the assumptions, such as: Inspired gas contains no carbon dioxide or water; Nitrogen (and any other gases except oxygen) in the inspired gas are in equilibrium with their dissolved states in the blood; Inspired and alveolar gases obey the ideal gas law; Carbon dioxide in the alveolar gas is in equilibrium with the arterial blood i.e., that the alveolar and arterial partial pressures are equal; and the alveolar gas is saturated with water. Alveolar gas equation is defined below:

$$p_AO_2 = \{(F_IO_2 * (P_{ATM} - pH_2O)) - (p_aCO_2\{1 - F_IO_2 * (1 - RQ)\})/(RQ)\} \tag{47}$$

If F_IO_2 is small, then ($F_IO_2 * (1 - RQ)\}$) is almost equal to zero. Therefore the equation can be simplified to:

$$p_AO_2 = \{(F_IO_2 * (P_{ATM} - pH_2O)) - (p_aCO_2)/(RQ)\} \tag{48}$$

Where:

Quantity	Description (Eqs. (7) and (8))	Sample value
p_AO_2	The alveolar partial pressure of oxygen (pO2)	107 mmHg (14.2 kPa)
F_1O_2	The fraction of inspired gas that is oxygen (expressed as a decimal).	0.21
P_{ATM}	The prevailing atmospheric pressure	760 mmHg (101 kPa)
pH_2O	The saturated vapor pressure of water at body temperature and the prevailing atmospheric pressure	47 mmHg (6.25 kPa)
p_aCO_2	The arterial partial pressure of carbon dioxide (pCO_2)	40 mmHg (4.79 kPa)
RQ (RER)	The respiratory quotient (Respiratory Exchange Ratio)	0.8

Note: Sample values are given for air at sea level at 37°C.

7.4.15 RESPIRATORY QUOTIENT

The respiratory quotient (RQ: or Respiratory coefficient or Respiratory Exchange Ratio) is a dimensionless number used in calculations of basal metabolic rate (BMR) when estimated from carbon dioxide production. It is measured using Ganong's Respirometer. It can be used in the alveolar gas equation. The respiratory quotient (RQ) is a ratio of eliminated CO_2 to the consumed O_2. The term "eliminated" refers to carbon dioxide (CO_2) removed ("eliminated") from the body. In this ratio, the CO_2 and O_2 must be in the same units and in quantities proportional to the number of molecules. Acceptable inputs would be either moles or volumes of gas at standard temperature and pressure. Many metabolized substances are compounds containing only the elements carbon, hydrogen, and oxygen. Examples include fatty acids, glycerol, carbohydrates, deamination products, and ethanol. For complete oxidation of such compounds, the chemical equation is given as follows:

$$C_xH_yO_z + (x + y/4 - (z/2))^* O_2 \longrightarrow (x)^*CO_2 + ((y/2))^*H_2O \quad (49)$$

Thus metabolism of this compound gives an RQ of $(x/(x + y/4 - z/2))$. The range of RQs for organisms in metabolic balance usually ranges from 1.0 (representing the value expected for pure carbohydrate oxidation) to ~0.7 (the value expected for pure fat oxidation). A mixed diet of fat and carbohydrate results in an average value between these numbers. An RQ may rise above 1.0 for an organism burning carbohydrate to produce or "lay down" fat (e.g., a bear preparing for hibernation). The RQ value corresponds to a caloric value for each liter (L) of CO_2 produced. If O_2 consumption numbers are available, they are usually used directly, as they are more direct and reliable estimates of energy production. Therefore, the RQ includes a contribution from the energy produced from protein. However, due to the complexity of the various ways in which different amino acids can be metabolized, no single RQ can be assigned to

the oxidation of protein in the diet. The respiratory quotients of some substances are given below:

Substance	RQ
Carbohydrates	1
Proteins	0.8–0.9
Ketones (eucaloric)	0.73
Ketones (hypocaloric)	0.66
Triolein (Fat)	0.7
Oleic Acid (Fat)	0.71
Tripalmitin (Fat)	0.7
Malic acid	1.33
Tartaric acid	1.6
Oxalic acid	4.0

Respiratory Exchange Ratio (RER) is a ratio between the amount of CO_2 produced and O_2 consumed in one breath (determined from comparing exhaled gasses to room air). The RER is also called RQ (Respiration quotient). In one breath, humans normally breathe in more molecules of oxygen (O_2) than they breathe out molecules of carbon dioxide (CO_2). RER is an indicator of which fuel (carbohydrate or fat) is being metabolized to supply the body with energy. RER is about 0.8 at rest with a modern diet. This value however, can exceed 1 during intense exercise, as CO_2 production by the working muscles becomes greater and more of the inhaled O_2 gets used rather than being expelled. During exercise, RER is less accurate because of factors including bicarbonate buffering of hydrogen ions, which affects the CO_2 levels being expelled by the respiratory system. The RER is commonly calculated in conjunction with exercise tests such as the "VO_2 – Maximum Test" and can be used as an indicator that the participants are nearing exhaustion and the limits of the cardio-respiratory system. An RER greater than 1.1 is often used as secondary end-point criteria of a VO_2 Max Test. An RER of 0.70 indicates that fat is the predominant fuel source; RER of 0.85 suggests a mix of fat and carbohydrates; and a value of 1.00 or above is indicative of carbohydrate being the predominant fuel source.

7.4.16 THE IMMERSED BOUNDARY (IB) METHOD

The IB method is a computational technique that was introduced by Peskin in the early 1970s as a method for studying a particular biofluid dynamics problem, namely the coupled motion of the blood filling the ventricles of the heart, the muscles of the heart wall, and the leaflets of the cardiac valves. Since that time, the method has been extended and applied to a wide variety of biofluid dynamics problems. Among others, these include platelet aggregation during blood clotting, swimming of aquatic flagellates, motion of the basilar membrane in the inner ear, the formation of bacterial biofilms, fluid motion in the afferent arterioles of the kidney, and pumping by ciliated arrays of tentacles on marine organisms. What these problems have in common with

the heart problem is that they involve the motion of a viscous incompressible fluid, the motion of one or more deformable elastic objects immersed in the fluid, and/or the motion of one or more deformable elastic surfaces that bound the fluid. Because the objects or surfaces are deformable and elastic, their motion is coupled to the fluid motion, *i.e.,* the motion of each affects the other. These, in fact, are features of essentially all biofluid dynamics problems. This situation is different from the traditional engineering fluid dynamics problem, which involves fluid motion through or around a rigid object of specified geometry.

The immersed boundary (IB) method has proved itself to be well suited for studying biofluid dynamics problems on scales ranging from subcellular to organ-size to organism-size. It has been used to look at hydrodynamic interactions among multiple organisms moving in the same fluid. The IB method takes into consideration both fluid viscosity and fluid inertia. In designing the original IB method, Peskin realized the advantages of describing the fluid variables and the immersed objects in different ways. The fluid variables (velocity, pressure, force density) are described in what is known as an Eulerian manner. One focuses on each point in space and asks how a quantity, like the fluid velocity, changes with time *at that point in space.* The objects are described in what is called a Lagrangian manner. Each material point on an object is tagged with a unique label, and one then tracks how the location of the material point *with a given label* changes as time advances and the system evolves. The state of the system at any time is given by the fluid velocity and pressure fields, and by the locations of the Lagrangian points which constitute the immersed objects. The essence of how the Immersed Boundary method computes the change in the system over a short time interval (or timestep) is as follows.

From the Lagrangian description of each immersed object, it is straight forward to determine how much the object has been stretched and deformed at the beginning of the timestep, and from this to calculate the elastic forces generated within the object. Since the object is in direct contact with the fluid, these forces affect the fluid motion. To calculate the effect of these forces on the fluid, they are transmitted from the elastic objects to the fluid, which immediately surrounds them, and thus contribute to the force density term in the fluid dynamics equations which drives the fluid motion. In fact, within the IB method, the fluid dynamics equations are solved everywhere (including inside the elastic objects) and the *only* way that the fluid 'feels' the presence of the elastic objects is through the force density just described. Contributions to the force density from the immersed objects are localized to regions immediately adjacent to the objects, and it in this way that the geometry of the objects makes itself felt. Once the fluid force density is known, the partial differential equations, which describe the fluid motion are solved to determine the new fluid velocity and pressure at each point of space. Finally, the fact that there is 'no-slip' between a point of a viscous fluid and a point of an object immediately adjacent to it gives an equation of motion for each immersed boundary point: The velocity of the immersed boundary point is just the velocity of the fluid at the same location. The immersed boundary point location is therefore changed by an amount equal to this velocity multiplied by the duration of the time step.

With IB method, despite the existence of irregular immersed boundaries, the fluid dynamics equations are solved on a regular finite difference grid. This allows an IB code to use fast numerical techniques to calculate the fluid velocities. By contrast, for the competing finite element method, a regular grid cannot be used to update the fluid velocities, and therefore, fast numerical solvers cannot be used. Furthermore, the motion of the immersed boundary would require that the shape of the finite elements change from time step to time step, and accuracy considerations would require that the entire domain be regridded periodically. The irregular grids require cumbersome data structures and the regridding is expensive. Similar drawbacks hold for finite difference methods, which use boundary-fitted coordinates (7).

7.5 HISTORICAL DEVELOPMENTS

7.5.1 RECENT HISTORICAL DEVELOPMENTS OF THE ARTIFICIAL LUNG

An artificial lung is a prosthetic device that is implanted into the body to replace biological lungs. A heart-lung machine is external, whereas the artificial lung is internal and is designed to take over the functions of the lungs for long periods of time rather than on a temporary basis. Recent developments include a device that uses small hollow fibers and pumping power of the heart to oxygenate blood. Physicians have been trying to adapt the heart-lung machine (See Chapter 2: Cardioplumonary Bypass Machine) for use as an artificial lung for people with severely damaged lungs and with severe emphyzema. The difficulty in developing a successful artificial lung is that our lungs and devices that mimic the lungs have a large surface area. When blood passes over a large artificial area, the blood clots can be formed. Designers seek to overcome this risk by giving patients powerful anticlotting drugs, but those can lead to unintended bleeding. It may be necessary for a person to receive artificial lungs if biological lungs become diseased or damaged beyond repair. Acute respiratory distress syndrome (ARDS) affected about 500,000 Americans in 2010. ARDS is characterized by a rapid and progressive breakdown of the lungs that impairs its ability to takein oxygen. ARDS is usually associated with the failure of other organs as well and can be caused by trauma, infection, severe pneumonia, or shock.

175 The Greek physician Galen used bellows to inflate the lungs of dead animals. Since then, scientists have attempted to replace the lung function with nonliving, inert materials.

1564 The first to report the successful inflation of the lungs by artificial means, which sustained life, was the Dutch physician Andreas Vesalius (1514–1564). He blew air into a tube of cane that had been implanted in an animal's trachea. By doing so, Vesalius was able to sustain the animal's life and observe the motions of the heart directly.

1670 John Mayow demonstrated that air is drawn into the lungs by enlarging the thoracic cavity. He built a model using bellows, inside which a bladder was inserted. Expanding the bellows caused air to fill the bladder. Compressing the bellows expelled air form the bladder. This was the principle of artificial respiration called "external

negative pressure ventilation" or ENPV that would lead to the invention of the iron lung and other respirators.

1793 The British surgeon John Hunter (1728–1793) – building upon Vesalius' work – invented the first device for artificially assisted respiration. He built an apparatus with double-chambered bellows (one chamber inflated the lungs, the other deflated them) and used it successfully in dogs.

1832 The Scottish physician John Dalziel developed a fully automated respirator in 1832. The principle behind this device was to cause subatmospheric pressures to be exerted outside of the thorax, thus allowing the more positive pressure of the atmosphere to inflate the lungs. A pair of bellows operated by a piston rod created the subatmospheric pressure.

1885 M. von Frey and M. Gruber (Leipzig) built and used the first artificial heart-lung apparatus for organ perfusion studies. The device relied on a thin film of blood and included heating and cooling chambers, manometers, and sampling outlets, which permited monitoring of temperature, pressure, and blood gases during perfusion.

1885 The first demonstration of a disc oxygenator: Blood was exposed to the atmosphere on rotating discs by Von Frey and Gruber. These pioneers noted the dangers of blood streaming, foaming and clotting.

1895 C. Jacobj (Germany) described complex organ perfusion apparatus that relied on donor lungs for gas exchange.

1915 N. Richards and C. Drinker (Philadelphia) reported use of a screen oxygenator for perfusion of isolated organs in which venous blood flows by gravity down a cloth in an oxygen-rich atmosphere.

1920s–1930s Research into developing extracorporeal oxygenation continued. Working independently, Brukhonenko in the USSR and John Heysham Gibbon in the USA demonstrated the feasibility of extracorporeal oxygenation. Brukhonenko used excised dog lungs while Gibbon used a direct contact drum type oxygenator, perfusing cats for up to 25 min in the 1930s.

1927 The first modern and practical respirator nicknamed the "iron lung" was invented by Harvard medical researchers Philip Drinker and Louis Agassiz Shaw. They used an iron box and two vacuum cleaners to build the prototype respirator. Almost the length of a subcompact car, the iron lung exerted a push-pull motion on the chest. The first iron lung was installed at Bellevue hospital in New York City. The first patients of the iron lung were polio sufferers with chest paralysis. Later, John Emerson improved upon Philip Drinker's invention and invented an iron lung at half the cost.

1928 H.H. Dale and E.H.J. Schuster (Hampstead, UK) described a double perfusion pump (for pulmonary and systemic circulations) relying on compressible diaphragms to circulate defibrinated blood during organ perfusion experiments. J. Gibbon, Jr. subsequently used this type of pump for early laboratory development of heart-lung apparatus.

1929 Dr. Philip Drinker and pediatric clinician Dr. Charles F. McKhann published an article entitled, "The Use of a New Apparatus for the Prolonged Administration of Artificial Respiration Part I: Fatal Case of Poliomyelitis," that reported successful clinical testing of the Drinker respirator.

1929 S. Brukhonenko and S. Tchetchuline (Russia) maintained temporary function of guillotined dogs' heads using donor lungs for gas exchange and a bellows-type pump for blood circulation.

1940s: The history of organ transplants began with several attempts that were unsuccessful due to transplant rejection. During the 1940s and 1950s, animal experimentation by various pioneers, including Vladimir Demikhov and Dominique Metras, first demonstrated that the procedure was technically feasible.

1953 In May of 1953, Gibbon conducted first clinical use of cardiopulmonary bypass operation for cardiac surgery. The oxygenator was of the stationary film type, in which oxygen was exposed to a film of blood as it flowed over a series of stainless steel plates. The disadvantages of direct contact between the blood and air were well recognized, and the less traumatic membrane oxygenator was developed to overcome these.

1955 First meeting of the American Society for Artificial Internal Organs is held at the Hotel Chelsea in Atlantic City, New Jersey with 67 founding members.

1955 Landmark publication: Clowes GHA Jr, Hopkins AL, Kolobow T., Oxygen diffusion through plastic films. Tr Am Soc Artif Intern Org 1:23–24, 1955.

1955 Landmark publication: Gibbon JH Jr., Artificial heart-lung machines: Chairman's address. Tr Am Soc Artif Intern Org 1:58–62, 1955.

1955 The first membrane artificial lung was demonstrated in 1955 by the group led by Willem Kolff.

1956 The first disposable membrane oxygenator removed the need for time consuming cleaning before reuse. No patent was filed as Kolff believed that doctors should make technology available to all, without mind to profit.

1956 Landmark publication: Clark LC Jr., Monitor and control of blood and tissue oxygenation. Tr Am Soc Artif Intern Org 2:41–45, 1956.

1956 G. Clowes (Cleveland) developed the first successful membrane oxygenator. By 1960s further laboratory research studying function and improvement of membrane lungs is undertaken by Kolobow, Peirce, Galletti, Bramson and Hill, Landé and Lillehei, Drinker and Bartlett.

1957 DeWall-Lillehei helix reservoir disposable bubble oxygenator was developed at the University of Minnesota and used in a series of 250 patients, which made cardiopulmonary bypass safe and reliable for other teams worldwide.

1960s and 1970s From 1963 to 1978, multiple attempts at lung transplantation failed because of rejection and problems with anastomotic bronchial healing. It was

only after the invention of the heart-lung machine, coupled with the development of immunosuppressive drugs such as cyclosporine, that organs such as the lungs could be transplanted with a reasonable chance of patient recovery.

1960 s The early artificial lungs used relatively impermeable polyethylene or Teflon homogeneous membranes, and it was not until more highly permeable silicone rubber membranes were introduced in the 1960s (and as hollow fibers in 1971) that the membrane oxygenator became commercially successful. The introduction of microporous hollow fibers with very low resistance to mass transfer revolutionized the design of membrane modules. The limiting factor to oxygenator performance was the blood resistance. Current designs of oxygenator typically use an extraluminal flow regime, where the blood flows outside the gas filled hollow fibers, for short-term life support, while only the homogeneous membranes are approved for long-term use.

1963 James Hardy of the University of Mississippi performed the first human lung transplant on June 11, 1963. Following a single-lung transplantation, the patient John Richard Russell survived for 18 days.

1965 The concept behind an implantable lung stemed from the first heart-lung machines developed for open heart surgery. It was proposed by Bodell et al. in 1965 as an implantable "third lung." It consisted of a 20-inch-long polytetrafluoroethylene graft and was successfully tested in dogs and sheep. Since then, scientists have improved its design, its gas exchange capabilities, its biocompatibility, and the implantation techniques. Scientific collaborations eventually yielded a consortium formed by the University of Michigan and MC3 Corporation, which conceived the BioLung. This prototype has sustained a sheep's life for 30 days 10 and more recently, it allowed animals to engage in moderate exercise. These studies have moved the artificial lung closer to clinical trials.

1972 J.D. Hill, T.G. O'Brien and others (in San Francisco) reported first successful clinical case using extracorporeal membrane oxygenation (ECMO) for respiratory failure.

1974 Landmark publication: Dobell WH, Mladejovsky MG, The directions for future research on sensory prostheses. Tr Am Soc Artif Intern Org 20:425–429, 1974.

1974 Lung Division of the National Heart and Lung Institute proposed a multicenter prospective randomized study of ECMO in adult respiratory failure; study began in 1975.

1975 Five different membrane oxygenators for ECMO were manufactured and used: the Kolobow Sci-Med, the Landé-Edwards, the Peirce-GE, the Bramson, and the Kolobow «Teflo."

1975 Landmark publication: Bartlett RH, Gazzaniga AB, Jeffries MR, Huxtable RF, Haiduc NJ and Fong SW, Extracorporeal membrane oxygenations (ECMO) cardiopulmonary support in infancy. Tr Am Soc Artif Intern Org 22:80–93, 1976.

1975 R.H. Bartlett, A.B. Gazzaniga and their colleagues (University of California, Irvine) reported first successful clinical case of neonatal ECMO.

1976 The United States Food and Drug Administration (FDA), established in 1931, began regulating medical devices with passage of the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act, which seeks to provide «reasonable assurance of safety and effectiveness» for all medical devices.

1978 BioMedicus Biopump disposable centrifugal pump (which was originally designed as an artificial heart by H. Kletschka) became commercially available as an alternative to the roller pump for cardiopulmonary bypass.

1981 Landmark publication: Malchesky PS, Asanuma Y, Smith JW, Kayashima K, Zawicki I, Werynski A, Blumenstein M, Nosé Y, Macromolecule removal from blood. Tr Am Soc Artif Intern Org 27:439–44, 1981.

1982 Extracorporeal CO_2 removal is described by Kolobow.

1982 The first successful transplant surgery involving the lungs was a heart-lung transplant, performed by Dr. Bruce Reitz of Stanford University on a woman who had idiopathic pulmonary hypertension.

1983 First successful long-term single lung transplant (Tom Hall) by Joel Cooper (Toronto)

1985 Crossover year during which one-half of all cardiopulmonary bypass procedures in the USA were performed with disposable membrane oxygenators, one-half with bubble oxygenators.

1986 First successful long-term double lung transplant (Ann Harrison) by Joel Cooper (Toronto)

1988 First successful long-term double lung transplant for cystic fibrosis by Joel Cooper (Toronto).

2001 After working for 14 years to develop a medical device for the lungs, **Brack Hattler** and his colleagues tested it in Europe in 2001. Hattler brought a group of transplant experts on the latest artificial lung technology for presentation at the meeting of International Society for Heart and Lung Transplantation in Vancouver, British Columbia. A professor of surgery at the University of Pittsburgh, Hattler indicates that "the U.S. Department of Defense first contacted him to work on developing a temporary lung during the days of the Gulf War. The US Department of Defense was concerned that Iraqi forces would use chemical weapons against allied forces. Those toxic chemicals could cause severe lung injuries, but not permanent ones. Hattler mentioned that "with this in mind, he with his collaborators developed a device for implanting inside a vein in the leg to supply oxygen to the blood. What we are doing is intercepting the blood before it arrives in the lungs. We can add oxygen and remove carbon dioxide while letting the lungs rest. External controls regulate the amount of oxygen supplied as well as the rate at which carbon dioxide is suctioned out of the blood. Although this device was the first major breakthrough in artificial lung technology, yet it is based on

earlier technology." The device by Hattler is much smaller, so the surface area is less, and the anticlotting drug heparin has actually been built into the device. This approach reduces the risk for clot formation. If Hattler's device (Figs. 16 and 17) is successful in human studies, Mockros says it will be a major advance in the world of artificial lungs (38). Several years ago a venture capital company introduced the concept with Intravascular Oxygenator (IVOX): A device that supplies oxygen to the veins. Lyle Mockros, PhD, Professor of Biomedical Engineering at North Western University in Chicago informs that the product was actually tested in humans, but was eventually abandoned when the developers ran out of money. Mockros says his group at North Western, as well as a third team at the University of Michigan, are concentrating their efforts on developing a more permanent artificial lung that could be used on longer-term while a patient waits to get a lung transplant. Current work is focused on devices that are wearable and are attached to the patient.

2010 Researchers create artificial lung that works with air rather than pure oxygen (Fig. 18): Researchers have created an artificial lung that uses air as a ventilating gas instead of pure oxygen – as is the case with current man-made lungs, which require heavy tanks of oxygen that limit their portability. The prototype device was built following the natural lung's design and tiny dimensions and the researchers say it has reached efficiencies akin to the genuine organ. With a volume roughly the same as a human lung, the device could be implanted into a person and even be driven by the heart.

2013 Researchers make super-realistic artificial lung tissue by **Levitating Cells** (Fig. 19): Traditionally, cell cultures have been made in a 2-D petri dish. Problem is, cells cultured flat do not act quite the same as cells made in 3-D cultures. Therefore, researchers from Rice University and Nano3D Biosciences started using magnetic levitation to get a 3-D culture. And now, using that tech, they have arranged four types of cells into super-realistic lung tissue. **This is how the levitation works**: Inert, magnetic nanoparticles are inserted into the cells, and researchers can manipulate them by using magnets–in this case, a magnetic "pen." That ability to tinker with the cells opens the door for more complicated cultures. The four-layered replication, of the lung's bronchiole tissue, is made from endothelial cells, smooth muscle cells, fibroblasts, and epithelial cells. Arranging those cells in the same way as lung tissue has never been done before, and the researchers claim that it is the closest anyone has gotten to real bronchiole tissue. As for practical applications: since the culture can be manipulated, researchers can better simulate how toxins would enter actual lungs, exposing certain layers to a toxin as they would be in the human body. Those better simulations could eventually lead to better treatments. For more details, the reader may consult:
<http://www.popsci.com/science/article/2013–01/researchers-make-better-lung-tissue-levitating-cells>

FIGURE 16 Artificial lung device (1).

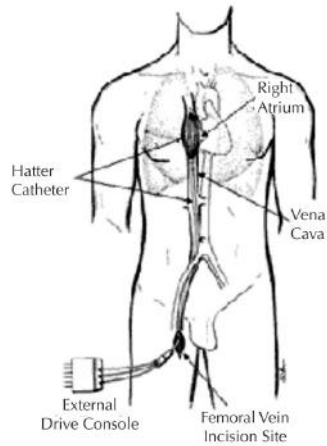


FIGURE 17 The Hatter respiratory catheter positioned in the human venous system (12).

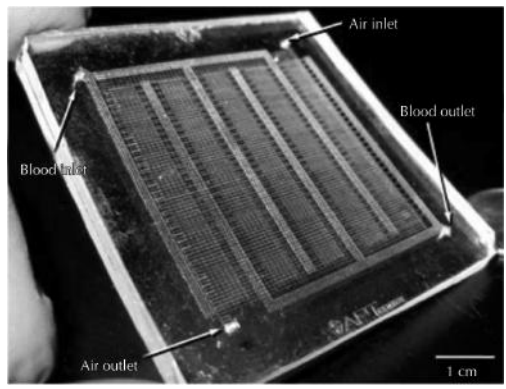


FIGURE 18 An artificial lung that works with air rather than pure oxygen.

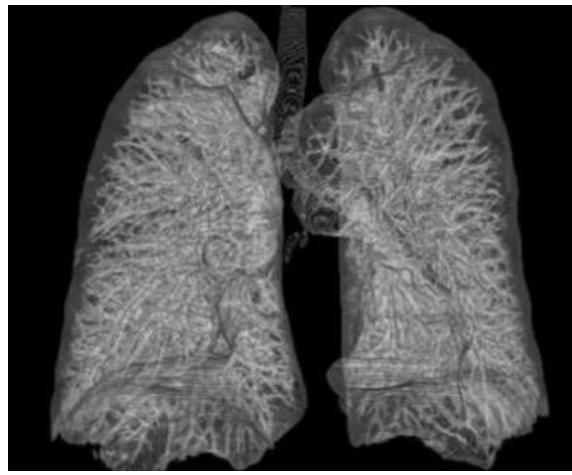


FIGURE 19 3-D Reconstruction of lungs (Andreas Heinemann/Wikimedia Commons).

7.6 CARDIOPULMONARY BYPASS

To repair most cardiac defects, the cardiothoracic surgeon requires a bloodless, motionless field in which to work. To achieve this, the motion of the heart and lungs must be stopped. For this to occur, there needs to be a means for blood to circulate throughout the body, delivering the nutrients and oxygen necessary for life, while the heart and lungs are not functioning. This is made possible through a process known as cardiopulmonary bypass (CPB, see Chapter 2). Clear polyvinyl chloride (PVC) tubing contains the blood as it is diverted from the body. Large bore catheters (called cannula) are placed in the right side of the heart, allowing the desaturated blood from the body to enter the cardiopulmonary bypass circuit. The PVC tubing runs through a mechanical pump that can be regulated to the proper cardiac output for a given patient. For example, a 5-year-old child has a much smaller cardiac output than an adult does; thus the pump must run at a higher rate for the adult patient than for the child. More PVC tubing delivers blood from the mechanical pump to a gas exchange device called an oxygenator, or artificial lung. The oxygenator performs the same job as the lungs: oxygenation of the blood as well as removal of carbon dioxide.

This reoxygenated blood is then returned to the body via another cannula placed in the aorta. In this way, cardiopulmonary bypass circuit permits the blood to bypass the heart and lungs, achieving the desired bloodless, motionless operative field and still supplying all the other organs of the body with a constant supply of oxygen and nutrient-rich blood.

The sum total of the mechanical pump, oxygenator, cannula and PVC tubing is often referred to as the heart-lung machine, or simply “the pump.” When a patient is being supported by a heart-lung machine, the patient is said to be “on bypass” or “on the pump.” Conversely, when a patient is taken off of this support, it is termed “off bypass” or “off the pump” (35).

7.6.1 CARDIOPULMONARY BYPASS RISKS

Although the origins of CPB can be traced back to the nineteenth century, the field has developed rapidly in the last 50 years. The first attempt to use a heart-lung machine for total CPB was carried out at the University of Minnesota in 1951. Since that time, CPB has become a standard, widely used, low-risk procedure. It is necessary to recognize some adverse effect when the circulation of the body is taken over artificially. CPB has a very wide range of effects on the body. All organ systems are affected by CPB: mainly the heart, lungs, brain and kidneys. These effects can range from mild to severe based on how sick the patient is before surgery, the length of time that a patient is supported by CPB and the complexity of the operation being performed.

The function of the heart may be compromised to a degree after bypass surgery. Some patients have subtle neurologic changes after bypass surgery. The occurrence of stroke or seizures during or after bypass remains low, but is a possibility. The kidney may experience damage ranging from decreased urine output to complete renal failure. Areas of the lung may fail to fully expand after bypass. This condition is known as atelectasis.

During CPB, the patients' blood makes contact with the foreign surfaces that make up the heart-lung machine, causing the patients' inflammatory system to be activated. Research has shown that this response can be damaging to certain tissues in the body. Due to the extra fluid volume needed to fill the CPB circuit, the patients' blood volume is diluted. This may require transfusion of blood products to the patient while on CPB and blood clotting abnormalities during the postoperative period.

The risk of serious complications related to being placed on cardiopulmonary support depends on the age of the patient, how ill they are at the time of the operation and the complexity of the surgery to be performed. In most cases, the risk is below one percent, but in higher complexity situations, it may be as high as 10 percent to 20 percent (35).

7.7 LUNG TRANSPLANTATION OR PULMONARY TRANSPLANTATION

Lung transplantation or pulmonary transplantation is a surgical procedure in which the diseased lungs are partially or totally replaced by lungs, which come from a donor. While lung transplants carry certain associated risks, they can also extend life expectancy and enhance the quality of life for end-stage pulmonary patients.

7.7.1 QUALIFYING CONDITIONS

Lung transplantation is the therapeutic measure of last resort for patients with end-stage lung disease who have exhausted all other available treatments without improvement. A variety of conditions may make such surgery necessary. As of 2005, the most common reasons for lung transplantation in the United States were:

- 27% Chronic obstructive pulmonary disease (COPD), including emphyzema;
- 16% Idiopathic pulmonary fibrosis;
- 14% Cystic fibrosis;
- 12% Idiopathic (formerly known as "primary") pulmonary hypertension;
- 5% Alpha 1-antitrypsin deficiency;
- 2% Replacing previously transplanted lungs that have since failed; and

- 24% Other causes, including bronchiectasis and sarcoidosis.

7.7.2 CONTRAINDICATIONS

Despite the severity of a patient's respiratory condition, certain preexisting conditions may make a person a poor candidate for lung transplantation:

- Concurrent chronic illness (e.g., congestive heart failure, kidney disease, liver disease);
- Current infections, including HIV and hepatitis, although more and more often Hepatitis C patients are both being transplanted and are also being used as donors if the recipient is Hepatitis C positive;
- Current or recent cancer;
- Current use of alcohol, tobacco, or illegal drugs;
- Age;
- Psychiatric conditions;
- History of noncompliance with medical instructions.

7.7.3 TRANSPLANT REQUIREMENTS

7.7.3.1 REQUIREMENTS FOR POTENTIAL DONORS

There are certain requirements for potential lung donors, due to the needs of the potential recipient. In the case of living donors, this is also in consideration of how the surgery will affect the donor:

- Healthy;
- Size match; the donated lung or lungs must be large enough to adequately oxygenate the patient, but small enough to fit within the recipient's chest cavity;
- Age;
- Blood type.

7.7.3.2 REQUIREMENTS FOR POTENTIAL RECIPIENTS

While a transplant center is free to set its own criteria for transplant candidates, certain requirements are generally agreed upon:

- End-stage lung disease;
- Has exhausted other available therapies without success;
- No other chronic medical conditions (e.g., heart, kidney, liver);
- No current infections or recent cancer. There are certain cases where preexisting infection is unavoidable, as with many patients with cystic fibrosis. In such cases, transplant centers, at their own discretion, may accept or reject patients with current infections of B. cepacia or MRSA;
- No HIV or hepatitis;
- No alcohol, smoking, or drug abuse;
- Within an acceptable weight range (marked undernourishment or obesity are both associated with increased mortality);
- Age;
- Acceptable psychological profile;
- Has social support system;

- Financially able to pay for expenses (where medical care is paid for directly by the patient); and
- Able to comply with posttransplant regimen. A lung transplant is a major operation, and following the transplant, the patient must be willing to adhere to a lifetime regimen of medications as well as continuing medical care.

7.7.4 MEDICAL TESTS FOR POTENTIAL TRANSPLANT CANDIDATES

Patients who are being considered for placement on the organ transplant list undergo extensive medical tests to evaluate their overall health status and suitability for transplant surgery.

- Blood typing; the recipient's blood type must match the donor's, due to antigens that are present on donated lungs. A mismatch of blood type can lead to a strong response by the immune system and subsequent rejection of the transplanted organs;
- Tissue typing; ideally, the lung tissue would also match as closely as possible between the donor and the recipient, but the desire to find a highly compatible donor organ must be balanced against the patient's immediacy of need;
- Chest X-ray – PA & LAT, to verify the size of the lungs and the chest cavity;
- Pulmonary function tests;
- CT Scan (High Resolution Thoracic and Abdominal);
- Bone mineral density scan;
- MUGA (Gated cardiac blood pool scan);
- Cardiac stress test (Dobutamine/Thallium scan);
- Ventilation/perfusion (V/Q) scan;
- Electrocardiogram;
- Cardiac catheterization;
- Echocardiogram; and
- Lung allocation score (LAS).

Before 2005, donor lungs within the United States were allocated by the United Network for Organ Sharing on a first-come, first-served basis to patients on the transplant list. This was replaced by the current system, in which prospective lung recipients of age of 12 and older are assigned LAS, which takes into account various measures of the patient's health. The new system allocates donated lungs according to the immediacy of need rather than how long a patient has been on the transplant list. Patients who are under the age of 12 are still given priority based on how long they have been on the transplant waitlist. The length of time spent on the list is also the deciding factor when multiple patients have the same lung allocation score. Patients who are accepted as good potential transplant candidates must carry a pager with them at all times in case a donor organ becomes available. These patients must also be prepared to move to their chosen transplant center at a moment's notice. Such patients may be encouraged to limit their travel within a certain geographical region in order to facilitate rapid transport to a transplant center.

7.7.5 TYPES OF LUNG TRANSPLANT

7.7.5.1 LOBE

A lobe transplant is a surgery in which part of a living donor's lung is removed and used to replace part of recipient's diseased lung. This procedure usually involves the donation of lobes from two different people, thus replacing a single lung in the recipient. Donors who have been properly screened should be able to maintain a normal quality of life despite the reduction in lung volume.

7.7.5.2 SINGLE-LUNG

Many patients can be helped by the transplantation of a single healthy lung. The donated lung typically comes from a donor who has been pronounced brain-dead.

In single-lung transplants, the lung with the worse pulmonary function is chosen for replacement. If both lungs function equally, then the right lung is usually favored for removal because it avoids having to maneuver around the heart, as would be required for excision of the left lung.

In a single-lung transplant the process starts out after the donor lung has been inspected and the decision to accept the donor lung for the patient has been made. An incision is generally made from under the shoulder blade around the chest, ending near the sternum. An alternate method involves an incision under the breastbone. In the case of a singular lung transplant the lung is collapsed, the blood vessels in the lung tied off, and the lung removed at the bronchial tube. The donor lung is placed, the blood vessels reattached, and the lung reinflated. To make sure the lung is satisfactory and to clear any remaining blood and mucus in the new lung a bronchoscopy will be performed. When the surgeons are satisfied with the performance of the lung the chest incision will be closed.

7.7.5.3 DOUBLE-LUNG

Certain patients may require both lungs to be replaced. This is especially the case for people with cystic fibrosis, due to the bacterial colonization commonly found within such patients' lungs; if only one lung were transplanted, bacteria in the native lung could potentially infect the newly transplanted organ.

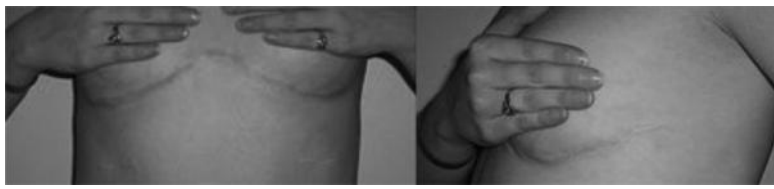


FIGURE 20 Incision scarring from a double lung transplant.

A double-lung transplant, also known as a bilateral transplant, can be executed either sequentially, en bloc, or simultaneously. Sequential is more common than en bloc. This is effectively like having two separate single-lung transplants done.

The transplantation process starts after the donor lungs are inspected and the decision to transplant has been made. An incision is then made from under the patient's armpit, around to the sternum, and then back towards the other armpit; this is known as a clamshell incision (Fig. 20). In the case of a sequential transplant the recipient's lung with the poorest lung functions is collapsed, the blood vessels tied off, and cut at the corresponding bronchi. The new lung is then placed and the blood vessels reattached. To make sure the lung is satisfactory before transplanting the other a bronchoscopy is performed. When the surgeons are satisfied with the performance of the new lung, surgery on the second lung will proceed. In 10% to 20% of double-lung transplants the patient is hooked up to a heart-lung machine which pumps blood for the body and supplies fresh oxygen.

7.7.5.4 HEART–LUNG TRANSPLANT

Some respiratory patients may also have severe cardiac disease which would necessitate a heart transplant. These patients can be treated by a surgery in which both lungs and the heart are replaced by organs from a donor or donors. A particularly involved example of this has been termed a "domino transplant" in the media. First performed in 1987, this type of transplant typically involves the transplantation of a heart and lungs into recipient A, whose own healthy heart is removed and transplanted into recipient B.

7.7.6 PROCEDURE

While the surgical details will depend on the type of transplant, many steps are common to all these procedures. Before operating on the recipient, the transplant surgeon inspects the donor lung (s) for signs of damage or disease. If the lung or lungs are approved, then the recipient is connected to an IV line and various monitoring equipment, including pulse oximetry. Pulse oximetry is a noninvasive method allowing the monitoring of the saturation of a patient's hemoglobin. The patient will be given general anesthesia, and a machine will breathe for him or her.

It takes about one hour for the preoperative preparation of the patient. A single lung transplant takes about four to eight hours, while a double lung transplant takes about six to 12 hr to complete. A history of prior chest surgery may complicate the procedure and require additional time.

7.7.7 POST-OPERATIVE CARE

Immediately following the surgery, the patient is placed in an intensive care unit for monitoring, normally for a period of a few days. The patient is put on a ventilator to assist breathing. Nutritional needs are generally met via total parenteral nutrition, although in some cases a nasogastric tube is sufficient for feeding. Chest tubes are put in so that excess fluids may be removed. Because the patient is confined to bed, a urinary catheter is used. IV lines are used in the neck and arm for monitoring and giving medications.

After a few days, barring any complications, the patient may be transferred to a general inpatient ward for further recovery. The average hospital stay following a lung transplant is generally one to three weeks, though complications may require a longer period of time.

After this stage, patients are typically required to attend rehabilitation gym for approximately 3 months to regain fitness. Light weights, exercise bike, treadmill, stretches and more are all a part of the rehabilitation program.

There may be a number of side effects following the surgery. Because certain nerve connections to the lungs are cut during the procedure, transplant recipients cannot feel the urge to cough or feel when their new lungs are becoming congested. They must therefore make conscious efforts to take deep breaths and cough in order to clear secretions from the lungs. Their heart rate responds less quickly to exertion due to the cutting of the vagus nerve that would normally help regulate it. They may also notice a change in their voice due to potential damage to the nerves that coordinate the vocal cords.

7.7.8 MISCELLANEOUS

Post-transplant patients are held from driving for the first three months pending an assessment of the patient's capacity to drive; this assessment is usually performed by an occupational therapist. Eyesight, physical ability to do simple actions such as check blind spots, wear a seat belt safely without the wound site being affected and hand eye coordination are all assessed.

Hygiene becomes more important in everyday living due to the immunosuppressant drugs, which are required every day to prevent transplant rejection. Lack of a strong immune system leaves transplant recipients vulnerable to infections. Care must be taken into food preparation and hygiene as gastroenteritis becomes more of a risk (Fig. 21).

FIGURE 21 Micrograph showing lung transplant rejection.

7.7.9 RISKS

As with any surgical procedure, there are risks of bleeding and infection. The newly transplanted lung itself may fail to properly heal and function. Because a large portion of the patient's body has been exposed to the outside air, sepsis is a possibility, so antibiotics will be given to try to prevent that. Other complications include posttransplant lymph-proliferative disorder: a form of lymphoma due to the immune suppressants, and gastrointestinal inflammation and ulceration of the stomach and esophagus.

Transplant rejection is a primary concern, both immediately after the surgery and continuing throughout the patient's life. Because the transplanted lung or lungs come from another person, the recipient's immune system will "see" it as an invader and attempt to neutralize it. Transplant rejection is a serious condition and must be treated as soon as possible.

Signs of rejection are: fever; flu-like symptoms, including chills, dizziness, nausea, general feeling of illness, night sweats; increased difficulty in breathing; worsening pulmonary test results; increased chest pain or tenderness; increase or decrease in body weight of more than 2 kilograms in a 24-hour period.

In order to prevent transplant rejection and subsequent damage to the new lung or lungs, patients must take a regimen of immunosuppressive drugs. Patients will normally have to take a combination of these medicines in order to combat the risk of rejection. This is a lifelong commitment, and must be strictly adhered to. The immunosuppressive regimen is begun just before or after surgery. Usually the regimen includes cyclosporine, azathioprine and corticosteroids, but as episodes of rejection may reoccur throughout a patient's life, the exact choices and dosages of immunosuppressants may have to be modified over time. Sometimes tacrolimus is given instead of cyclosporine and mycophenolate mofetil instead of azathioprine.

The immunosuppressants that are needed to prevent organ rejection also introduce some risks. By lowering the body's ability to mount an immune reaction, these medicines also increase the chances of infection. Antibiotics may be prescribed in order to treat or prevent such infections. In turn, infection may increase the risk of rejection, and generally an interaction may prevail between both risks. Certain medications may also have nephrotoxic or other potentially harmful side-effects. Other medications may also be prescribed in order to help alleviate these side effects. There is also the risk that a patient may have an allergic reaction to the medications. Close follow-up care is required in order to balance the benefits of these drugs versus their potential risks.

Chronic rejection, meaning repeated bouts of rejection symptoms beyond the first year after the transplant surgery, occurs in approximately 50% of patients. Such chronic rejection presents itself as bronchiolitis obliterans, or less frequently, atherosclerosis.

7.7.10 PROGNOSIS

Transplanted lungs can last three to five years before showing signs of failure. The following statistics are based on data from 2008. The source data made no distinction between living and deceased donor organs, nor was any distinction made between lobar, single, and double lung transplants.

Transplant type	1 year survival	5 years survival	10 years survival
Lung transplant	83.6%	53.4%	28.4%
Heart-lung transplant	73.8%	46.5%	28.3%

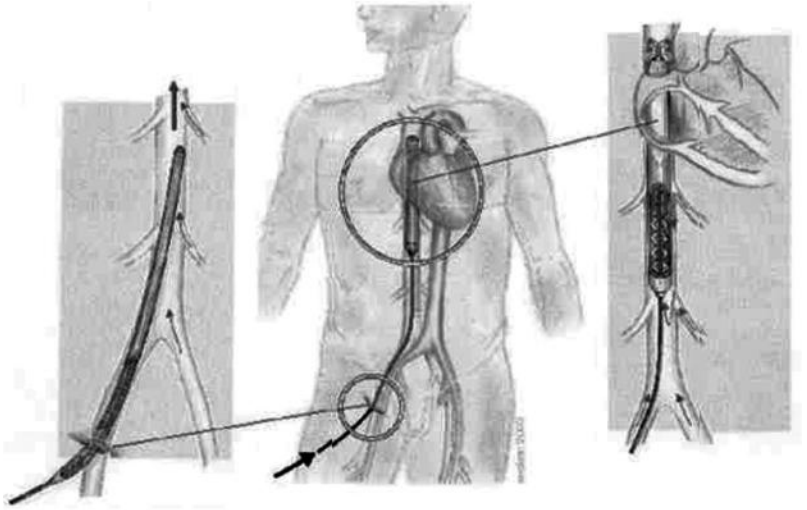


FIGURE 22 Anatomical position of the HIMOX (11).

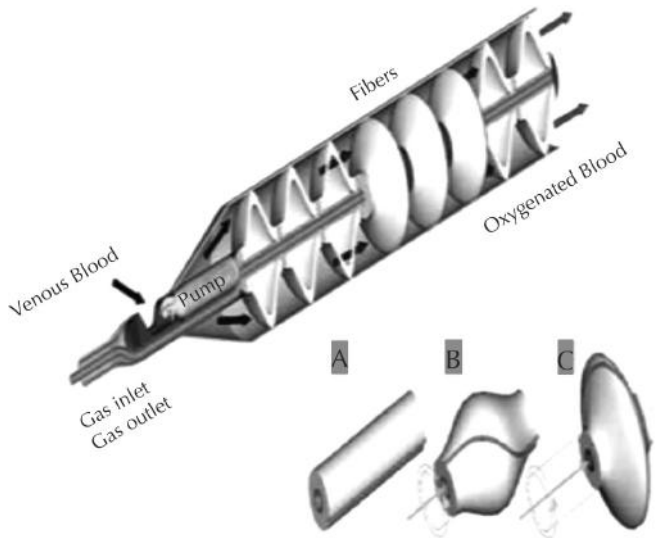


FIGURE 23 Three dimensional view representation of the intravascular oxygenator HIMOX (11).

7.8 PRINCIPLES OF OPERATION

7.8.1 AN ARTIFICIAL LUNG PREPARED WITH CULTURE SYSTEM

The three-dimentional view and the anatomical position of the HIMOX are shown in Figs. 22 and 23. Crafted from fibers of polyethylene, the catheter rests in the vena cava, the main channel for blood on its way back to the heart. To maximize gas

exchange, the fibers surround a balloon that can inflate up to 300 times a minute. The entire bundle (Figs. 24 and 25) is threaded up a leg artery into the chest and is hooked up to a computer monitor that is located near the bed of the patient (39).

1. PRINCIPAL MATERIALS

This section emphasizes methods of production of an artificial lung system comprising of an endothelial cell layer, an epithelial cell layer and an artificial microporous membrane. Endothelial cell layer can include microvascular endothelial cell line, human lung endothelial cell line, human liver endothelial cell line and human umbilical cord cell line. However, there are many nonhuman endothelial cells available to study on nonhuman pathogens. Human epithelial cells refer to a type of cell, which forms on the outer surface of the body and lines organs, cavities and mucosal surfaces. Such cells can comprise the human endometrial carcinoma cell line, the human cervical carcinoma cell line, the human lung carcinoma cell line and the human larynx carcinoma cell line as well as primary epithelial cell cultures, among others.

The system consists of two cell layers (specifically, an endothelial layer and an alveolar epithelial layer) oriented to either side of and in direct contact with a membrane (an artificial microporous membrane). In this section, we shall focus on methods for constructing an artificial organ with culture system and on the presence of chemical and pathogens substances inside the artificial system (39).

2. PRINCIPLES OF OPERATION AND BACKGROUND OF AN ARTIFICIAL LUNG PREPARED WITH CULTURE SYSTEM

Tuberculosis brought a new focus to study respiratory diseases. In specific, tuberculosis (Mycobacterium tuberculosis) infects 2 billions people worldwide and causes more than 3 million deaths annually. The proliferation of tuberculosis in the United States with an evident increase in incidence of multidrug resistant strains is in part due to increases in acquired or reactivated disease in patients infected with the HIV virus. Better understanding of pathogenic mechanisms is needed to search for improved methods of prevention and control.

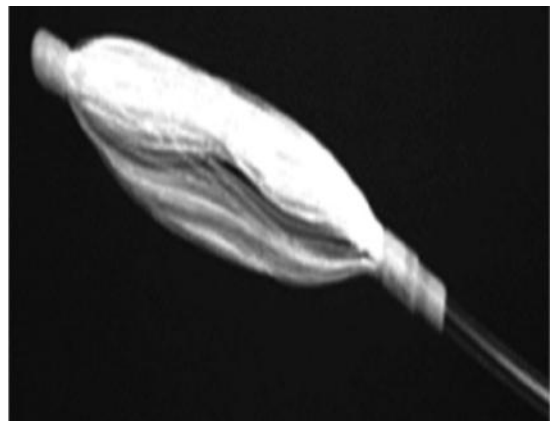


FIGURE 24 Single Membrane (3).

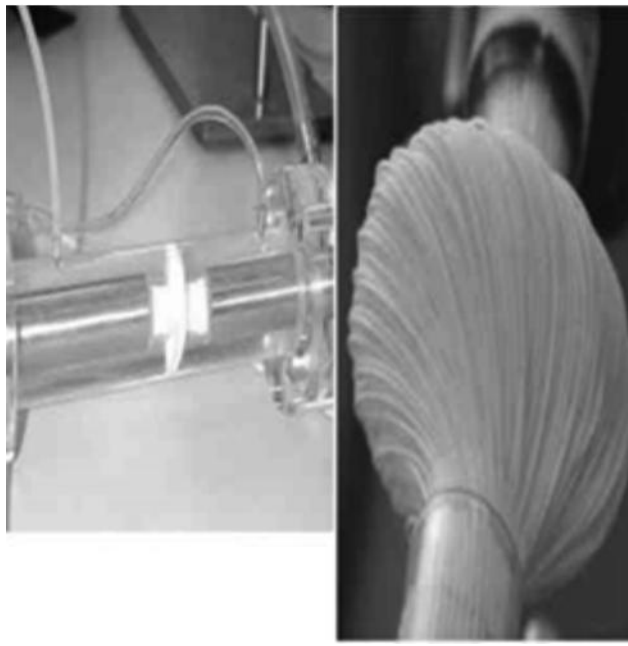


FIGURE 25 A single fiber bundle fixed within a casing (11).

Researches have found that intracellular growth occurs within the cultured human lung endothelial cells. This proves that even a few organisms inhaled into alveolar tissue could multiply significantly before penetrating the epithelial cells, lining the alveolar spaces, and into the blood stream. Alveolar epithelial cells form on the outer surface of the alveolar sacs in the lungs. Such alveolar cells include primary lung pneumocytes, human lung carcinoma cell line, human larynx and lung carcinoma cell line.

This artificial system can be used in other applications but specifically for the artificial lung application. The system requires incorporation of an endothelial and alveolar epithelial cell layers on a microporous membrane to study the process of attachment and passage that happens when the pulmonary pathogen agent or foreign substance makes its way from the alveolar surface, through the epithelial cells and into the circulatory system.

The culture a layer of epithelial cells directly over a layer of endothelial tissue has been attempted. The initial results indicated that the epithelial cells outgrew the endothelial cells. This problem was overcomed by establishing a layer of endothelial cells on an artificial microporous membrane suspended in a tissue culture. It was expected that nutrients in the fluid medium would remain accessible to the endothelial cells even after the epithelial cell layer was formed on top of it.

It is believed that the greater exposure to nutrients might prevent the underlying endothelial cell layer from being starved and killed by the epithelial cells. However, researchers have been amazed with the unexpected fact that upon addition of epithelial cells to the layer of endothelial cells growing on the membrane, the endothelial cells migrated through the pores of the membrane and grew into a layer of cells on the opposite

side of it, successfully establishing stable layers of two different cell types very close to each other.

An artificial microporous membrane can have a thickness of between 10 to 200 microns with a preferable thickness range of 15 to 30 microns with uniform pores within the membrane. Diameter may range between 0.45 to 10 microns, preferably with a diameter of 3 microns. This membrane can be composed partially or totally of a synthetic material or can comprise of a naturally occurring material in a molecular or ultrastructural arrangement not normally found in nature.

Synthetic materials used in membranes are fluoropolymer, polycarbonate, polyester, nitrocellulose, cellulose, acetate, polycarbonate and polystirene, among others. The membrane is usually coated with biocompatible material on one or both sides to facilitate attachment of cells to the membrane surfaces. These materials can be collagen, laminin, proteoglycan or vitronectin among others.

This specific artificial lung system can be effectively used for the study of the attachment and invasion factors contributing to Mycobacterium tuberculosis pathogenesis and leads itself to similar studies with other pathologic agents. Epidemic, mutants and sporadic cases can also be examined as they pass through these artificial system to investigate which genes are turned on or off in reaction to environmental changes and changes in the requirements for bacteria survival.

3. FUNCTION, COMPOSITION, AND SIGNIFICANCE OF AN ARTIFICIAL LUNG PREPARED WITH CULTURE TISSUE

The culture tissue technology is obtained compressing an endothelial tissue layer, an alveolar epithelial tissue layer and an artificial microporous membrane, having pores therein, disposed between with the endothelial cell later and alveolar epithelial cell layer and in direct contact with each other such that the membrane has an endothelial side and epithelial side. This artificial system is contained in a vessel compressing an upper chamber into which the epithelial side faces and containing the alveolar epithelial cell layer, and a lower chamber into which the endothelial side faces and containing the endothelial cells. For tissue culture, the vessels can be made in the form of tubes, bottles, chambers, flasks, vials or tissue culture.

The membrane can be supported above the bottom of the vessel at any distance from the bottom of the vessel as long as the membrane can be covered by a fluid medium within the vessel and a sufficient amount of space exists between the endothelial cell layers and the bottom of the vessel to allow nutrients in the fluid medium to contact the endothelial cell layer. The artificial mircoporous membrane can be supported a distance from of the vessel by number of ways:

- Use of a plastic frame.
- Suspension of the membrane in a vessel.
- Use of gel or wire baskets.

The conditions under which the endothelial cells form a confluent layer of cells on the epithelial side of the membrane can comprise maintaining the endothelial basal medium with about 7.0% fetal bovine serum at 37°C in about 5.0% carbon dioxide for eight days. The other physiologically balanced medium can be used, providing it contains adequate growth factors for endothelial cells.

The fetal bovine serum concentration can range from 0 to 20% in the medium. The cells can be effectively incubated at a temperature of 25°C to 42°C and a CO_2 concentration of 2% to 8%. The endothelial cells can be cultured from six to ten days prior to the addition of the epithelial cells.

A "basement membrane material" implies a porous extra cellular matrix which functions as a support structure in a manner similar to the way basement membrane material functions as a support structure in whole organs. The artificial lung system can further include a layer of basement membrane material in direct contact with the epithelial side of the membrane and with the alveolar epithelial cell layer. This basement membrane material is included during construction of artificial lung organ system and is place in direct contact with the apical surface of the membrane prior to addition of the endothelial cells. The "apical surface" is the side of the membrane that faces away from the bottom of the vessel.

When the system is completed, the apical surface coincides with the epithelial side. After that, the endothelial cells then establish a confluent monolayer on the surface of the basement membrane material and subsequently migrate through both the basement membrane material and membrane to the basal surface of the membrane upon addition of the epithelial cells to the apical surface.

The basal surface is the side of the membrane which faces the bottom of the vessel. It coincides with the endothelial side when the artificial lung is completed. Thus, the basement membrane material coats the membrane but does not block the migration of endothelial cells, pathogens or other chemical substances through the pores of the membrane.

The biocompatible materials described herein can form the present basement membrane. The material type includes an extra cellular matrix composed of laminin, collagen, fibronectin or any combination.

This cellular matrix material can also be recommended for the elaboration of any other type of human organ. Nevertheless, some system could require more specific studies to identify the most adequate material to include in a particular type of artificial organ.

Studies using artificial lung system prototypes have been used as models to evaluate the effects of various extra cellular matrix material on the integrity of the cell layers, the ability of pathogens and chemical substances to pass through the system as well as the effects of various extra cellular matrix materials on the mechanisms of transport of pathogens and chemical substances through the system.

In the artificial lung system, alveolar macrophages can be present in the upper chamber and can either be suspended in liquid medium above the alveolar epithelial cell layer or in contact with the alveolar epithelial cells of the alveolar epithelial cell layer.

The existence of alveolar macrophanges on the epithelial side of the membrane more closely mimics the environment within the living lung, in which alveolar macrophages are present within the alveolar sacs. Therefore, the construction of the artificial lung can include placing alveolar macrophages in the upper chamber containing the alveolar epithelial cells after establishing the artificial lung.

Usually, the alveolar macrophages can be obtained from the alveolar fluid obtained by alveolar lavage. One way of doing this is by placing a tube into the lung and the alveoli can be sprayed with sterile saline which can then be suctioned from the lung as alveolar lavage fluid. Then the alveolar macrophages can be separated from other cells and particulate materials in the alveolar lavage fluid by techniques for separation of macrophages.

7.8.2 THE IMPORTANCE OF AN ARTIFICIAL LUNG MODEL

For the purpose of mimicking more closely the environment of living alveolar sacs, the construction of artificial lung systems can include placing alveolar fluid into upper chamber after establishment of the artificial lung system. The alveolar fluid is a highly viscous solution comprising secreted surfactants, saline and other serum proteins (Table 4). In artificial lung system, white blood cells can be present in the lower chamber, either suspended in liquid medium around the endothelial cell layer or in contact with the endothelial cells of the endothelial cell layer.

TABLE 4 Alveolar fluid characteristics (43).

Structure	**Alveoli**
Relations	Component of lungs, works-with capillaries.
Behavior	Gas passes from high concentration to low across semipermeable membrane.
Property	Elastic, semi permeable.
Function	Gas exchange.

Chemical agents and toxins that can be introduced to an artificial lung system can include: tar, nicotine, coal dust, asbestos, and oxygen radicals among others. These chemical compounds can be introduced into artificial lung system on either the epithelial or endothelial side, depending on where a given substance would be known to interact with lung tissue in the body. The effects of toxic oxygen radicals, which would enter the alveolar sacs through inhalation, can be studied by introducing these molecules into the artificial lung system on the epithelial side of the membrane.

Alternatively, the affects of nitrous oxide, which is produced by white blood cells, can be studied by introducing this compound on both the epithelial and the endothelial sides of the membrane. An example of a substance is red blood cells, which would be present in the in vivo environment in blood vessels lined with endothelial cells.

Thus, construction of the artificial lung system can further include placing white blood cells in the lower chamber containing the endothelial cells, after establishment of the artificial lung system. To provide an even more physiologically accurate model of the environment of the living lung, the upper chamber can contain no or a minimal amount of fluid medium. The humidity in the upper chamber can be maintained at a level which keeps the epithelial cells healthy and/or mimics the internal environment of the alveolar sac.

This is done, because the epithelial cells lining the alveolar sacs of the lungs are not normally submerged in fluid in a healthy physiological state. Pathogens and other

chemical substances in solid, liquid or gaseous state can be introduced into the upper chamber and the affects of these agents on the artificial lung system under these conditions can be determined.

The construction of the artificial lung system can further include placing a means for maintaining movement of fluid medium in the lower chamber after establishment of the artificial lung. This can include a magnetic stir bar and a flow chamber, among others. For example, a magnetic stir bar mimics the movement of blood through the blood vessels. As an example, red blood cells (sickled red blood cells) can be added to the system to study the interactions of these cells with the cell layers of the artificial organ system.

An additional asset of this artificial lung system is its adaptability for the study of a wide variety of organisms. Several epithelial cell lines have been used in the system, which has been used to show differences between a virulent and an avirulent strain of the influenza bacteria biogroup aegyptius. The endothelial layer can be a different vascular line, such as human umbilical vein cells, even more relevant to the pathogenesis of a given organism.

An artificial organ system is a useful tool to screen chemicals (including drugs, medicaments or chemical toxins, among others) to determine the movement of these substances through the artificial system. Such studies can also provide useful information on the effectiveness of applications such as drug treatments and vaccines whose mechanism of action involves blocking the binding of certain pathogens to host cells. In the artificial lung system, such chemicals can be, for example, antibiotics, antiviral drugs, or drugs to treat lung diseases such as cystic fibrosis, asbestos, etc., as well as vaccine and lytic peptide therapeutics against lung and upper respiratory pathogens, among others.

The chemicals of interest can be detected on the endothelial side of the membrane, either in the contact with the endothelial cells or in the liquid medium in the lower chamber, or within the artificial organ system by methods well known. For example, immunofluorescent and immunohistochemical reagents can be applied to the cells of the artificial organ system to identify and locate the presence of various substances added to the artificial organ system.

7.8.3 HATTLER RESPIRATORY CATHETER

The idea for an artificial lung was developed in 1984, when Brack Hattler had two patients rushed into the emergency room with severe damage to the lungs, their only hope of survival was artificial lungs. Despite Hattler's efforts, both patients died a few days later. Since then, Hattler dedicated himself to developing an artificial lung. This artificial lung was targeted toward patients with acute respiratory distress syndrome, pneumonia, chronic lung disease, patients in need of organ transplants, and patients in intensive care units.

The standard care today is the extracorporeal membrane oxygenators, which can be bulky and expensive, and causes life-threatening complications in more than half of its users. The IMO (Intravenous or Implantable Membrane Oxygenator) device has been designed to oxygenate the blood before it gets to the lungs, which allows the lung

to rest and recover. The IMO device is to be only used for patients that have a chance to reverse their respiratory problems.

IMO consisted of about 1000 hollow fiber membranes over the span of several feet in length. Oxygen enters through an external tube and flows through the fibers under vacuum. The oxygen in the fibers diffuses through tiny pores in the fiber wall into the blood. At the same time carbon dioxide diffuses out of the fibers and exist through a second tube. The central balloon pulsates about 300 times a minutes to move the fibers and mix the blood. As this balloon inflates and deflates blood is drawn across the fibers. This provides little impedance to the blood flow returning to the heart. The IMO device is implanted through the vein in the leg, using percutaneous insertion (as done for angioplasty catheters and intraaortic balloon pumps). The device is then positioned into the Vena Cava. An advantage of the IMO device is that it allows the lungs to do very little work, therefore letting the lungs rest and heal. When compared to ventilators that make the lungs work twice as hard due to the constant expanding and compressing to oxygenate the blood. This device is expected to benefit up to 700,000 patients a year. The patients will range from people with serious respiratory damage, acute emphyzema, and severe asthma to victims of drowning and fire accidents to chemical weapons. The commercial product may be available in 2004 (15).

Intravenous Membrane Oxygenator: Artificial lungs have been undergoing development since the 1980s. The intravenous oxygenator (IVOX) was first implanted in humans (Figs. 26 and 27). IVOX was only able to provide 30% of the basal gas exchange requirements in the best case, while at least 50% was required for IVOX to be deemed clinically useful.

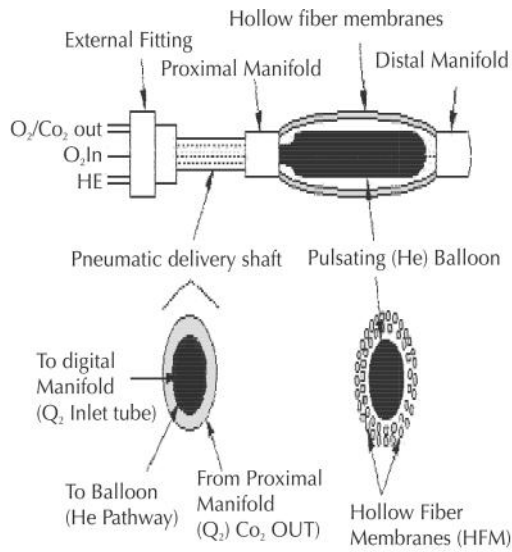


FIGURE 26 The Intravenous membrane oxygenator device (20).

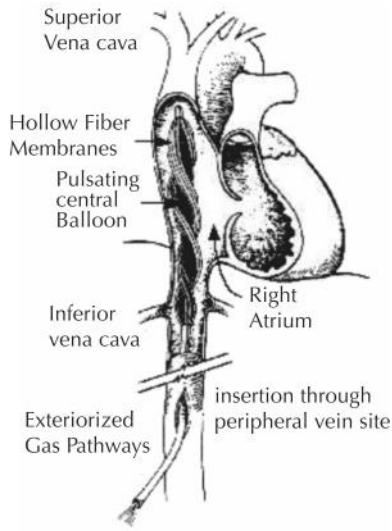


FIGURE 27 Inserted intravenous membrane oxygenator device (21).

A second generation ILAD, the Hattler Respiratory Catheter, was developed by Dr. Brack Hattler, University of Pittsburg, USA. The Hattler Catheter was able to provide 50% of the gas exchange requirements. There are limitations of the amount of gas exchange that these types of devices can provide as there is a limited volume of intravascular space in which the device resides (20).

7.8.4 LESSONS LEARNED FROM INTRAVASCULAR OXYGENATOR (IO)

Intravascular oxygenation (IO), based on implantation of a membrane oxygenator within the vena cava, is a promizing alternative to extracorporeal oxygenation for treating patients with ARDS. Compared to extracorporeal oxygenation, IO has a smaller blood-contact surface, reduces the size and the depth of the insertion as well as the risk of infection, and sets the priming volume to zero. The purpose is to increase the fiber surface and flow, enhancing gas transfer, without impairing venous return to the heart. HIMOX (High Integrated Intravascular Membrane Oxygenator) presents a new compact fiber arrangement associated with high total gas exchange. A micro axial pump is integrated into the oxygenator within a deformable casing, in order to compensate for flow resistance and to avoid blood stagnation. Key features of HIMOX are several bundles of gas permeable fibers, which can slide on a catheter, assuming two main configurations: Bundles lie parallel to the catheter during insertion, making the oxygenator long and narrow. HIMOX fits into the small insertion of the femoral vein. Bundles are compressed and twisted within the vena cava. Due to compression, fibers spread outwards, making the oxygenator short and wide. The spreaded and twisted configuration allows filling the volume in the vena cava, maximizing implantable fiber surface. Moreover, the fibers assume a tightly packed cross flow configuration, enhancing blood mixing (11).

7.8.5 HOLLOW FIBER MEMBRANE

The Intravenous Membrane Oxygenator (IMO) has been undergoing research development in the Artificial Lung Laboratory at the University of Pittsburgh under prior grants from the Army Medical Research and Material Command. The IMO promised to augment incomplete respiration in soldiers and civilians suffering from acute respiratory failure. The IMO is an artificial lung catheter that is inserted through the femoral vein in the leg and placed within the vena cava. The end of the catheter contains a bundle of hollow fiber membranes (Figs 26 and 27) connected through gas pathways in the shank of the catheter to an external O_2 source. Oxygen diffuses through the permeable hollow fibers of the IMO into blood and CO_2 diffuses out of the blood into the fibers and is removed from the exit gas pathway of the device. A balloon within the fiber bundle, pulsated with helium gas through another gas pathway, mixes the blood effectively over the fiber surfaces to improve the rate of gas exchange. The IMO has reached an advanced stage of research development in the laboratory, has gone through substantial prototype evolution and performance improvements, and has been tested extensively in the bench and in animal implants. The purpose and scope of the work done over the past year in the NTEC program was to finalize the IMO catheter performance and design specifications (i.e., to complete technology development on the IMO) in preparation for technology transfer and the formal product development that would lead to human clinical trials.

Technology development of the IMO) was completed during the NTEC Year 1 grant program. The principal tasks involved: Finalizing the gas exchange specification for the IMO for clinical use, optimizing the gas pathways of the IMO and fiber selection to minimize insertion size, and developing biocompatible coatings to prevent plasma wetting and to minimize thrombus formation. The IMO was prepared for technology transfer to a medical device company which is continuing with the formal product development of the IMO required to gain FDA approval to begin human clinical trials. Once available for human clinical use, the IMO will be an attractive alternative therapy for acute respiratory failure (ARF) associated with battlefield trauma and is of great benefit in civilian applications. ARF arises from a variety of insults, which leave the lungs unable to maintain adequate gas exchange. Respiratory failure and death usually follow unless the lungs are rested and allowed to recover from the insult. Respiratory failure can occur in soldiers in combat and noncombat situations suffering from trauma, shock, infections, smoke inhalation, or exposed to chemical agents injurious to the lungs. Likewise, the civilian population is not immune from chemical or biological attack, and in the event of such attack the need for pulmonary support for a large number of victims will exist in an emergency setting. Researches expect that the IMO will become a key medical device deployed in these situations (21).

7.8.6 HOLLOW FIBER MEMBRANE PERMEABILITY ANALYSIS

The fundamental gas exchange element of the IMO is the hollow fiber membrane (HFM). The capacity of the IMO to deliver oxygen and remove carbon dioxide from venous blood flow is determined by the resistance to gas flux of the HFM wall and of the blood phase flowing over the exterior of the fiber surface. Typically, in extracorporeal oxygenators the dominant mass transfer resistance is that of the blood phase, and

the HFM wall resistance is assumed to be negligible. However, an intravenous oxygenator must reside within the vena cava and not restrict blood flow returning to the heart, thus the total fiber surface area is constrained to be approximately 4–6 times less than that of conventional extracorporeal devices. Thus design strategies for meeting gas transfer requirements in intravenous oxygenators rely on mechanisms for reducing blood-side mass transfer resistance. The natural result of a significant reduction in the blood-side mass transfer resistance is to increase the effect of the fiber wall resistance on overall device permeability.

Because of the greater potential effect that the HFM (Figs. 28 and 29) permeability has on the gas transfer performance of an IVMO, selection of an appropriate fiber is critical. Not only must the fiber permeability be greater than the desired device permeability so as not to limit gas transfer performance, but it must also remain stable for extended periods of time. Contemporary extracorporeal membrane oxygenators are predominantly comprised of microporous-walled hollow fiber membranes, which provide greater diffusional capability than "true" membrane fiber constructions. However, after several hours of use, the performance of microporous oxygenators deteriorates due to fiber wetting and subsequent serum leakage through the pores and into the gas flow path. Strategies to resist or block wetting include using fibers with markedly reduced pore size, or alternatively, using a composite fiber consisting of a thin nonporous (true) membrane layered over or sandwiched within a standard microporous wall. In both cases, the very strategies meant to resist fluid wetting also diminish fiber wall permeability. This is especially so in composite fibers, where the nonporous polymer layer can represent an appreciable impediment to diffusion (13).

To evaluate HFMs, a simple apparatus and methodology was developed for measuring HFM permeability in a gas-liquid environment (Fig. 28). This procedure has the capability of studying a variety of fiber types in any liquid of interest, such as blood. The central component of the measurement procedure is a diffusion chamber, which consists of a parallel arrangement of hollow fiber membranes submerged in a stirred liquid bath of fixed volume (300 cc). The apparatus and methodology developed to make these measurements requires relatively small liquid volumes, and so would lend itself well to fiber permeability studies in blood serum, plasma, or anticoagulated whole blood.

The methodology for extracting membrane permeability from the measurement of the overall system permeability is based on isolating the effect of the liquid side mass transfer resistance from the membrane resistance. This is done by measuring the system permeability at increasing levels of liquid side mixing which results in reduced liquid side resistance. Membrane permeability can then be determined by extrapolating the system permeability, K, to infinite mixing where the liquid side resistance is effectively zero, and the system permeability is equal to the membrane permeability, i.e., $K = Km$.

A detailed analysis of the validity of the measurements obtained with the diffusion chamber is described in an article entitled, "Gas Permeability of hollow fiber membranes in a gas-liquid system" (Journal Membrane Science, Volume 117, 1996); and A novel method for measuring hollow fiber membrane permeability in a gas-liquid system (American Society of Artificial Internal Organs, ASAIO, Journal, Volume 42,

1996).” The diffusion chamber is currently being used to compare the permeabilities and wetting characteristics of uncoated microporous HFMs versus the same fiber coated with an ultrathin nonporous polymer layer fabricated by Bend Research. Contrary to intuition, it has been found that in a gas-liquid environment, a coated fiber can have greater oxygen permeability than the same fiber, uncoated (13).

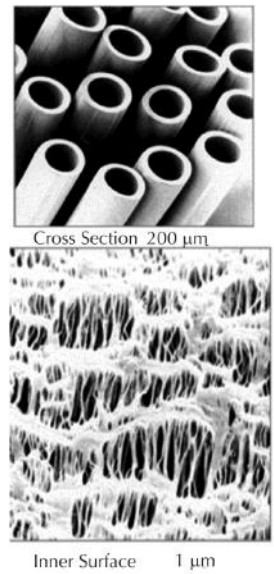


FIGURE 28 Hollow fiber membrane (13).

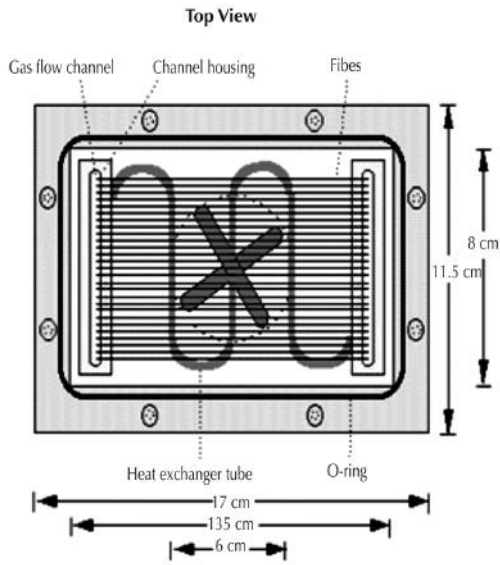


FIGURE 29 An apparatus for measuring HFM permeability in a gas-liquid environment (13).

7.8.7 INTRATHORACIC ARTIFICIAL LUNG

Researchers at North-western University – USA are developing an artificial lung that can be implanted inside the chest cavity and attached directly to the artery connecting the heart to the lung. The researchers have succeeded in preserving lung function in an animal model for 24 hr with the new device, intended primarily as a "bridge to transplant" for patients awaiting lung transplants and as a treatment for acute lung failure.

The implantable artificial lung contains a bundle of fibers that exchange oxygen for carbon dioxide. The "lung" is attached directly to the main pulmonary artery on the right side of the heart and returns the oxygenated blood to the left atrium of the heart. It can be adjusted so that a portion of the blood continues to circulate through the impaired natural lungs.

It marks the first 24-hour use of an implanted artificial lung in an animal model to date, according to Lyle F. Mockros, Professor of Biomedical Engineering at North-Western's University. He has coauthored a report published in the September-October issue of the American Society of Artificial Internal Organs Journal: "The development of a successful, implantable artificial lung will increase the therapeutic options for children and adults with severe lung disease."

According to Dr. Robert Bartlett, Professor of Surgery at the University of Michigan and a leading authority on the development of artificial lungs, there is very good cooperation among the five groups to develop an implantable artificial lung. There groups are at: Penn State Medical Center; the University of Pittsburgh; in Salt Lake City; University of Michigan and North Western University.

The new device is called an implantable, intrathoracic artificial lung, or **ITAL**. It consists of a bundle of fibers with tiny holes that allow oxygen to move into the bloodstream and carbon dioxide to move back into the fibers. The devices are being implanted by Carl L. Backer, M.D., assistant professor of surgery. Keith E. Cook, a graduate student in biomedical engineering and lead author of the journal article, was primarily responsible for designing the new ITAL, which is smaller and more compliant than previous designs. The new device has a much higher oxygen and carbon dioxide delivery rate, providing for the first time the full gas-transfer requirements for a person at rest, he added. The artificial lung research is considered particularly urgent now because of the current success of lung transplant operations. Thousands of additional patients could benefit from lung transplants who do not have appropriately matched donor lungs available, and they die while waiting. The only current treatment for end-stage lung failure is lung transplantation. An additional 150,000 Americans acquire acute respiratory distress syndrome each year, with a mortality rate of over 50 percent (40).

7.9 VENTILATOR THERAPY

The acute respiratory distress syndrome (ARDS) continues as a contributor to the morbidity and mortality of patients in intensive care units throughout the world, imparting tremendous human and financial costs. During the last 10 years there has been a decline in ARDS mortality without a clear explanation. The American-European Consensus Committee on ARDS was formed to reevaluate the standards for the ICU care of patients with acute lung injury (ALI), with regard to ventilatory strategies, the

more promizing pharmacologic agents, and the definition and quantification of pathologic features of ALI that require resolution. It was felt that the definition of strategies for the clinical design and coordination of studies between centers and continents was becoming increasingly important to facilitate the study of various new therapies for ARDS.

Despite advances in supportive care, the mortality rate in patients with ARDS is considered high, and generally in excess of 50%. Large multicenter prospective controlled randomized trials are needed to provide definitive answers concerning the efficacy of new and existing therapies. These trials generally must address two considerations: Basic research that links the proposed new treatment to important pathophysiologic components of ARDS; and The risk-benefit ratio of the treatment to be tested. It may be naive to assume that any single therapy will be a "magic" bullet to treat all aspects of ARDS.

This second American European Consensus Conference on ARDS (18) was organized in an attempt to analyze the pathophysiologic mechanisms of lung damage as they relate to mechanical ventilation strategies and to promizing agents, which may ultimately be shown to have utility in the treatment or prevention of ALI and ARDS. In addition, the increasing costs of care associated with only marginally perceived additional benefits of novel therapies prompted the Consensus Committee to reevaluate the current treatment of ALI/ARDS. In order to analyze the recovery from ALI, an attempt was made to define the clinical and pathologic features of AL1 that require resolution and how these should be defined and quantified. The members of the Consensus Committee were divided into subcommittees, each of which was charged with discussing and developing a position paper on at least one aspect of the problem. These position papers were presented to the entire Committee for comments and discussion. When the Committee reached agreement, specific modifications were made to the position papers. The following subcommittee reports is a result of this consensus process (ARDS Report #1333):

Although ARDS has previously been considered a problem of diffuse lung injury and a generalized increase of tissue recoil, it now appears that the radiographic, densitometric, and mechanical consequences of ARDS are heterogeneous. In severe cases, the inflation capacity of the lungs may be less than one third of normal. The compliance and fragility of tissues comprising the aerated compartment in ARDS are likely to bemore functionally normal than previously envisioned, especially in the earliest phase of this disease. Computed values for airway and tissue resistance are elevated in ARDS, an observation that is perhaps best explained by the reduced number of patent airways. The refractory hypoxemia of AL1 can be enhanced by supplementing inspired O_2 and by raizing mean and end-expiratory alveolar pressures. Each of these interventions, however, has associated risks and benefits. Animal studies have shown that high fractions of inspired O_2 and high cycling pressures are potentially injurious, especially when applied over extended periods superimposed on preexisting damage, or combined with other injurious agents. Widely held objectives of ventilation in the setting of AL1 have given priority to normalizing arterial blood gases and avoiding depression of cardiac output. Until recently respiratory system pressures in humans have been monitored but not tightly constrained. Flow-controlled, volume-cycled

ventilation, using tidal volumes of l0–15 mL/kg, has previously been the standard of practice in the management of ARDS and most other problems of adult ventilatory support. Mean airway pressure, as a clinically measurable reflection of mean alveolar pressure, relates fundamentally to oxygen exchange, cardiovascular performance, and fluid retention under conditions of *passive inflation*. Positive end-expiratory pressure (PEEP) has been used to increase end-expiratory transalveolar pressure and volume, and thereby to improve gas exchange. The alveolar pressure that determines aerated volume at end-expiration is the sum of deliberately applied PEEP and that may arise by dynamic hyperinflation (auto or intrinsic PEEP).

The latter may often be significant in ALU/ARDS due to high minute ventilation, the use of extended inspiratory time fractions, and the elevated resistance of the native airway, endotracheal tube, and exhalation valve. All forms of barotrauma described in the pediatric literature, including interstitial emphyzema, tension cysts, systemic gas embolism, and damage similar to bronchopulmonary dysplasia, have now been recognized in patients with ARDS. In experimental animals, the choice of ventilatory pattern influences the morphology of normal and previously injured tissue. From these animal studies, it is suspected that excessive *regional* volumes are damaging, whether produced by positive or negative pressure.

Ventilatory patterns that apply high transalveolar stretching forces cause or extend tissue edema and damage in experimental animals. Recent work strongly suggests that regional overdistention is commonly produced in patients with ARDS by static airway pressures greater than 30 cm H_2O, a pressure level known to cause damage in sheep when sustained for more than a few hours. Although excessive tidal volume must be avoided, animal studies suggest that periodic inflations with a relatively large and sustained volume may be needed to avoid collapse of unstable lung units when very small tidal volumes (< 4–5 mL/kg) are used. Judging from the substantial delay to peak incidence of pneumothorax, the lung appears to be able to withstand exposure to somewhat higher forces in the earliest phase of human ARDS without *radiographically evident* barotraumas. Later in the course of illness the strong collagen infrastructure of the lung degrades unevenly, so that similar pressures are more likely to result in overt alveolar disruption (e.g., pneumothorax, pneumomediatinum, gas cyst formation). Animal studies indicate that failure to preserve a certain minimum end-expiratory transalveolar pressure in the early phase of ARDS may intensify preexisting alveolar damage, especially when high tidal volumes are used. Indeed, the shear forces associated with tidal collapse and reinflation of injured alveolar tissues may be responsible for an important component of ventilator-induced lung damage. The end-expiratory pressure required to avert widespread alveolar collapse varies with the hydrostatic forces applied to the lung. Consequently, a higher pressure is required in patients to prevent atelectasis in dependent regions than in the regions more superior.

Gravitational factors, therefore, help to explain the strikingly dependent distribution of radiographic infiltrates shortly following the onset of lung injury, as well as reversal of these infiltrates and improved arterial oxygenation in the prone position. In experimental animal studies, total PEEP sufficient to place the tidal volume above the initial low compliance region of the static pressurevolume relationship of the respiratory system (Pflex) appears to attenuate the severe hemorrhagic edema otherwise

induced by high ventilating pressures. Stress failure of the pulmonary capillaries with resulting pressures that exceed 40–90 mm Hg, depending on animal species. Although the relationship of this observation to the hemorrhagic edema of experimental (ventilator- induced) lung injury remains unclear, transcapillary mechanical forces of comparable magnitude may be generated in ARDS when high tidal volumes and peak static tidal pressures are used. High vascular pressures and blood flows may also be important determinants of lung injury. Certain adjuncts to conventional ventilation, such as nitric oxide inhalation tracheal gas insufflation, and perfluorocarbon-associated (partial liquid) ventilation, currently show promise to improve transpulmonary gas exchange; other approaches, such as surfactant administration and inhaled prostacyclin may eventually prove beneficial.

Controversies detailed clinical information is not available for guidance regarding the maximally safe peak and mean alveolar pressures that can be applied for extended periods without inducing alveolar damage or retarding healing. Although failure to preserve a certain minimum end-expiratory transalveolar pressure has been shown experimentally to intensify preexisting alveolar damage this phenomenon has not yet been clearly demonstrated in humans.

Consequently, expert opinion differs on whether applying the least PEEP that accomplishes adequate gas exchange or the guarantee of some minimal value of end-expiratory alveolar pressure is the best course to follow within the first few days of the disease process. Periodic application of sustained high inflating pressures to recruit unstable lung units continues to be advocated by some highly knowledgeable investigators, especially when small tidal volumes are used, as in high frequency ventilation. The appropriate tidal volume to use undoubtedly varies with the level of PEEP. There is no consensus regarding the contribution of vascular pressures, position changes, infection, inspired oxygen concentration, and other clinical variables on the incidence and intensity of ventilatorinduced lung injury. Allowing Pace, to rise to supernormal values (permissive hypercapnia) appears to be an effective strategy for limiting the need for ventilatory pressure. The full effects of hypercapnia on such important variables as gas exchange, cardiovascular dynamics, and tissue edema have yet to be determined in this setting.

Elevated fraction of inspired oxygen (FlO and high ventilatory pressures are often required to achieve near complete saturation of arterial blood with oxygen. The conditions (if any) under which arterial O_2 saturation can be allowed to fall to subnormal values without unacceptable clinical consequences have not yet been delineated. There is no clear consensus regarding the most appropriate indicator of regional or global adequacy/inadequacy of O_2 delivery (dysoxia) for routine clinical use. The combinations of O_2 concentration and exposure duration that produce significant lung damage have not been firmly established in the setting of ARDS, and may well vary with disease severity and individual susceptibility. Similarly, although a considerable body of experimental data has been accumulated, detailed information is not yet available regarding which ventilation pressures and patterns of ventilation are safe to apply for extended periods. In the absence of definitive data obtained in a clinical context, some knowledgeable practitioners increase lung volume, whereas others prefer to use higher inspired fractions of O_2 rather than increase peak, mean, and end-expiratory

airway pressures. Although absolute agreement was not reached, the majority of the consensus conferences believe that limiting airway pressure takes precedence over limiting FIO.

A very recent prospective randomized study from a single institution indicates improved lung mechanics, gas exchange, and respiratory mortality by following a strategy emphasizing ventilation with reduced alveolar pressure and tidal volume. Yet, one well-conducted prospective comparison of a modern approach that included inverse ratio ventilation and extrapulmonary CO_2 removal (when necessary) to a more conventional strategy was unable to detect a significant outcome difference between them. Most clinicians recognize the need to control maximum alveolar pressure and are cognizant of a connection between mean alveolar pressure and arterial OZ tension; however, there is no uniformity of opinion regarding the best mode and method of ventilatory support. Specifically, whether different methods for achieving a similar mean airway pressure (such as high-level PEEP) and inverse ratio ventilation differ with respect to risks and benefits has not been adequately examined.

The extent to which spontaneous (versus controlled) ventilation should be encouraged has also been an area of uncertainty. There is renewed interest in high-frequency ventilation applied at an appropriate mean lung volume as a ventilatory strategy for ARDS, but the basis of this enthusiasm remains primarily theoretical and experimental at this time. Several recent studies have addressed the topic of risk and benefit for manipulation of oxygen delivery. Because mechanical ventilation can benefit or impair O_2 delivery, such observations may hold implications for its implementation (6).

7.10 HOW DOES ARTIFICIAL LUNG WORK?

Artificial lungs or lung assist devices have the potential to benefit about 150,000 patients annually who have acute respiratory problems. Lung replacement is one of the possible treatment, but there are not enough natural lung donors. The Intravenous Membrane Oxygenator (IMO) device is an "engineered" device that performs the main function of the natural lung (blood oxygenation and carbon dioxide removal) but operates differently than the natural lung. The IMO is an intracorporeal device implanted within the vena cava that consists of hundred of hollow fiber membranes and an inflating-deflating balloon to generate a secondary flow across the fiber in order to enhance the oxygen transfer rates. The design of IMO devices was optimized by performing Direct Numerical Simulations (DNS) of oxygen transfer and hemodynamics, to reduce the costly time-consuming experimental design cycle. Specifically, the objective was to obtain a better understanding of the basic mechanisms responsible for mass transfer enhancement induced by cross-pulsating flow, quantify the effect of the frequency and amplitude of the balloon pulsation on the efficiency of the oxygenation and carbon dioxide removal, and quantify the risk of blood damage and coagulation. A computational model of the IMO device was developed and performed large scale DNS of the conservation of mass, momentum and species equations with a stationary and a pulsating balloon (5).

7.10.1 ARTIFICIAL LUNGS: DIRECT CONTACT TYPE

This class of artificial lung is employed in the majority of open-heart surgical procedures, and may be further classified accordingly to the mode of presentation of the blood to the ventilating gas. The subtypes are bubble, film and disc. In the film type, a thin layer of blood flows over a solid surface, which is situated within the gas phase. This thin-film effect is also achieved in the disc oxygenator by continuously forming a blood layer on a series of circular discs pick up blood from are reservoir in which they are partially immersed. The film of blood formed on the remaining disc area is exposed to the ventilating gas. Although the film and disc units have been widely used in the past, they have been superseded by more easily operated bubble systems. Figure 27 shows the predicted performance of the system in a scaled-up device.

7.10.2 ARTIFICIAL LUNG: INDIRECT-CONTACT TYPE-MEMBRANE

All membrane oxygenators in clinical use at present have sheet-membrane geometries as opposed to tubular configurations. The membrane materials employed are homogenous polymers (e.g., silicone rubber) with or without fabric reinforcement, or polymer with micropores (e.g., polytetrafluoroethylene). Devices with pure laminar flow are fluid-limited in performance for existing membrane materials. However, laminar-flow units are preferred for clinical use since they are generally easier to operate than systems, which employ convective mixing to enhance performance. The descriptions of several clinical membrane oxygenators, which are principally fluid-limited in performance, are given followed by a discussion of two experimental devices with convectively mixed blood flow.

a. Pneumatic Delivery System

The existing pneumatic delivery system is being thoroughly studied to assess its functionality in a scaled-up device (Figs. 30 and 31). The delivery system has three main functions: to supply oxygen to the fiber bundle; to remove the oxygen and carbon dioxide exhaust gases from the fiber bundle; and to allow the delivery of an oscillating flow of helium to actuate the balloon. For maximal oxygen exchange, the pressure losses before the fiber bundle should be minimized. Any loss of pressure before the fiber bundle will detract from the driving gradient for oxygen exchange. The pressure losses after the fiber bundle should also be as small as possible to reduce the load on the driving system. To ensure full filling and emptying of the balloon, a low resistance helium pathway is required.

The pneumatic delivery system performs well in the prototypes currently being tested. However, several problems are likely to arise when the device is resized for human use. The length of the fiber bundle will be doubled, thus adding length to the oxygen delivery pathway and increasing the pressure losses before the fiber bundle. Also, the size of the balloon will be increased from 30 to 70 cc. At a given beat rate, the flow rate of helium required to fill a 70 cc. balloon will be 2.3 times larger than the flow rate required to fill the 30 cc. balloons. In order for the drive system now in use to provide helium at this rate, the resistance of the helium pathway may need to be reduced.

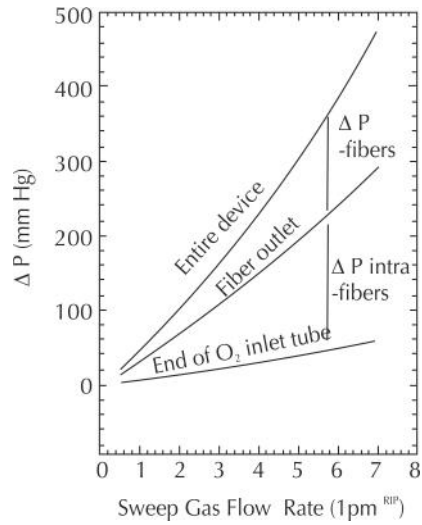


FIGURE 30 Predicted performance of the system in a scaled-up device (22).

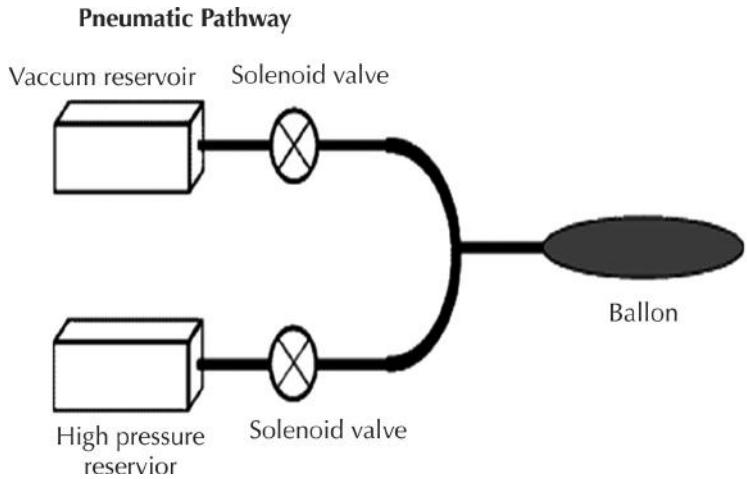


FIGURE 31 Pneumatic pathway (23).

Testing of the device has shown that the drive system being used to power the balloon fails to fully inflate and deflate the balloon above a beat rate of 180 beats per minute. Therefore, the resistance of the helium pathway must be decreased if a larger balloon is to be pulsed effectively.

It is likely that the concentric tube design now in use will be replaced by a multilumen catheter. Preliminary calculations have indicated that a multilumen catheter would both improve the pneumatic performance of the delivery system and ease the manufacture and assembly of the device (22). Table 5 shows normal values for respiratory mechanics.

TABLE 5 Normal respiratory mechanics values (26).

Parameter	Adult	Neonatal
Respiratory Rate	10–15 breaths/minute	30–40 breaths/minute
Tidal Volume	7–10 mL/Kg	5–7 mL/Kg
Minute Ventilation	5–10 liters/min.	200–300 ml/Kg/min.
Dynamic Compliance	25–50 mL/cm H_2O	1–2 mL/cm H_2O/Kg
Airway Resistance	2–5 cm H_2O/L/S	25–50 cm H_2O/L/S
Work of Breathing (Insp.)	0.3-0.6 joules/liter	1.2-2.1 joules/liter
Intrinsic PEEP	0 cm H_2O	2–3 cm H_2O
Respiratory Drive PO.1	2–4 cm H_2O	0.7–1.5 cm H_2O

FIGURE 32 Respiratory mechanics module (25).

FIGURE 33 EZFlow sensors (25).

FIGURE 34 METEOR handheld monitor (25).

FIGURE 35 Respiratory mechanics evaluation Kit (25).

b. Drive System For A Balloon

Throughout the development of the IMO, balloon inflation and deflation was controlled with an intraaortic balloon pump (IABP) console. This console was designed to pulse the balloon at the same rate as the human heart beat (around 80 beats per minute), however, gas exchange in the IMO improves as the beat rate increases and maximizes at approximately 150 beats per minute. Unfortunately, the IABP console cannot completely fill and empty the balloon at higher beat rates, necessitating the development of an improved drive system for the IMO (23).

The main goal of the drive system is to fill and empty the balloon as quickly as possible. This will require both a high-pressure reservoir and a vacuum reservoir, each connected to the balloon via a solenoid valve. The balloon is filled by opening the valve to the high-pressure reservoir, and emptied by opening the valve to the low-pressure reservoir (Fig. 31). The balloon pulsation rate is limited by the amount of time it takes to fill and empty the balloon. If the pulsation rate is too high, the balloon will not inflate and deflate completely, and the subsequent decrease in blood mixing will result in inadequate oxygenation. The amount of time required depends on the driving pressure (the pressures in the high pressure and vacuum reservoirs) and the pressure drop across the system. Because it is possible to apply several atmospheres of positive pressure but only draw one atmosphere of vacuum, emptying the balloon will take longer than filling it and will become a limiting factor of the balloon pulsation rate. The ultimate goal of the drive system to fill and empty the balloon quickly enough that oxygenation is not limited by the balloon pulsation rate.

7.10.3 RESPIRATORY MECHANICS PRODUCTS

Mechanical ventilators deliver gas at a pressure and flow, which results in a change in patient lung volume. Before waveform graphics became integral components of ventilator systems, ventilator monitoring was restricted to reading the ventilator's controls, digital monitors and mechanical gauges as well as physical assessments. Detailed analysis of the patient/ventilator interface was, therefore, impossible. Technological advances now permit continuous Respiratory Mechanics monitoring, including graphic display of gas flow, volume, and airway pressure. Output waveforms are useful tools to study the characteristics of ventilator operation and provide a graphic display of the various modes of ventilation. Waveform analysis can be used to optimize mechanical ventilatory support and analyze ventilator incidents and alarm conditions. Using this technology, it is now possible to shape the form of ventilatory support to improve patient-ventilator synchrony, reduce work of breathing, and calculate a variety of physiologic parameters related to Respiratory Mechanics.

There are several products available to assist the medical device manufacturer in adding Respiratory Mechanics monitoring to ventilators or stand-alone monitors.

CPT's OEM Respiratory Mechanics system is a small, low power and fully digital system that is available with or without a purge (Figs. 32 to 35).

The system uses a proprietary smart connector, which interfaces to the disposable EZ-Flow flow sensor. This chassis mount connector tells the system that a sensor is properly placed, identifies the type of sensor and maintains tubing polarity.

- The module is based upon a Philips 80C51 XA 16 bit microprocessor.
- Pressures are measured by two piezoresistive bridge based differential pressure transducers: 5″ H_2O and 5 psi ranges. These transducers are internally compensated for temperature, but additional compensation is made from a digital temperature device on the board, placed between the transducers.
- The system uses a 24 bit A/D converter to interface transducer output to the microprocessor. The standard system has two microsolenoid valves for atmospheric zeroing and the optional purge function.
- Power regulation on the board allows for input voltages to range from 4 V – 9 V. The purge system consumes approximately 1000 mW.
- Bi-directional RS232 serial communication is used to interface to the module. The specific protocol is available upon request.
- Clearance above the board can be no less than 0.6 inch; below board clearance needed is 0.4 inch.
- The purge system is for long-term, continuous monitoring – purgeless for less than four hours of monitoring. The purge function maintains pressure line patency.

The Respiratory Mechanics Module is available in the marketfor evaluation and product development (25). Negative and positive pressure ventilators are shown in Figs. 36 and 37.

7.10.4 BALLOON PULSATION DYNAMICS

Balloon motion significantly enhances the oxygen exchange performance of the IMO device by providing active mixing. Inflation and deflation of the balloon is driven by

an Intra-Aortic Balloon Pump (IABP), which delivers helium through a long, narrow catheter to the balloon. The catheter must also supply oxygen to and exhaust carbon dioxide from the fibers, meaning that only a fraction of the catheter's lumen is available for helium flow. There is an upper limit to pulsation frequency, which depends upon the mechanics of the delivery catheter (the physical size of the helium pathway), the power of the drive system, and ultimately the fragility of red blood cells (pumping too fast *in vivo* could lead to the destruction of red blood cells) (19).

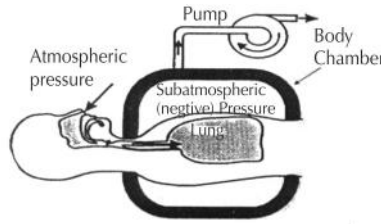


FIGURE 36 A simplified illustration of negative – pressure ventilator (29).

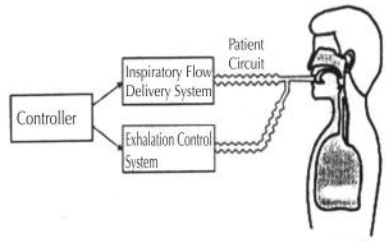


FIGURE 37 A simplified diagram of the functional block of a positive – pressure ventilator (29).

7.11 AEROSOL DELIVERY OF DRUGS

For both lung and systemic diseases, aerosol delivery of drugs into the lungs can often offer substantial advantages over other routes of administration. In the intensive care unit, however, the artificial airway can be a substantial barrier to aerosol delivery, so clinicians must pay careful attention to the ventilator pattern, the delivery gas humidity/density, the device characteristics, and the circuit/tube properties. When those are optimized, aerosol delivery from a nebulizer or metered-dose inhaler and through an endotracheal tube can begin to approach that seen in a nonintubated patient. Novel approaches, such as generating the aerosol within the airway, offer the opportunity to greatly increase deposition efficiency and focal drug targeting in intubated patients.

Medication delivery into the airways of intubated patients can offer substantial advantages over parenteral or oral administration routes. For medications targeted at lung diseases, a higher therapeutic index can be achieved with drugs delivered directly to the site of intended action, with little or no systemic exposure. The lung can also be a useful portal for medications designed for systemic targets, because drugs that can

easily pass through the alveolar-capillary interface (e.g., insulin) can be exposed to a large lung surface area in contact with the entire cardiac output.

Effective aerosolized medication delivery into the lungs of intubated patients depends on many of the same factors important in nonintubated patients: efficient device output, small particle size, low-velocity gas flow, large inspired volume, and breath-hold at end inspiration. The intubated patient, however, offers additional challenges: the artificial airway is a different geometry than the natural airway; the aerosol delivery system is generally attached to the ventilator circuit in which heat, humidification, and bias gas flows may be present; pressure gradients down the airways are different than during spontaneous breathing; and the required mechanical ventilatory pattern may not be ideal for aerosol delivery (6).

7.12 RECENT INVESTIGATIONS

7.12.1 IMPROVED ARTIFICIAL LUNGS FOR RESPIRATORY SUPPORT

DR. WILLIAM J. FEDERSPIEL is developing next generation artificial lung devices for treatment of patients with respiratory failure. The artificial lungs under development are composed of bundles of hollow fiber membranes fabricated into various modules and catheters that can be perfused with blood intracoporeally or extracorporeally. The hollow fiber membranes are manifolded to gas pathways that allow oxygen gas to flow through the insides of the hollow fibers, thus driving the diffusion of oxygen into the bloodstream and of carbon dioxide outside of the blood stream. Artificial lungs are traditionally mass transfer devices limited due to diffusional boundary layers that arise on the fiber surfaces. His specific potential projects include research and development on:

1. A balloon pulsated respiratory catheter;
2. A self-pumping extracorporeal emergency respiratory support lung;
3. Biohybrid microfabricated artificial lung modules;
4. Hollow fibers with bioactive and mechanically active coatings, and
5. Aspects of control and monitoring consoles for artificial lungs (37).

7.12.2 A LUNG TECHNOLOGY: A BREATH OF FRESH AIR

While life supporting, ventilators can damage a person's lungs, throat and sinuses, cause pneumonia and create a dependency on the machine. Weaning can actually more than double the time the patient is connected to the artificial device. Unfortunately, clinical experience at medical centers across the country shows that the longer a patient is connected to a mechanical ventilator, the greater their chances of dying. So it is a great challenge (37).

7.12.3 THE HATTLER CATHETER—A NEW WAY TO OXYGENATE BLOOD

Dr. Brack Hattler and Dr. William Federspiel are working with $9 million grants from US Department of Defence and additional investments of $3.6 million from Angels and Innovation Works. A Lung Technologies has developed the Hattler™ Catheter: a more gentle, equally effective and less costly way of delivering oxygen to the bloodstream and transporting carbon dioxide back out. With an experienced management team in place, the company is working to move the Hattler Catheter through clinical

trials, FDA approvals and into ICUs and emergency rooms across the country and around the world (12).

7.12.4 THE MARKET NEED

Every year, approximately 400,000 patients in the U.S. alone (1 million worldwide) require mechanical ventilation as a result of acute respiratory failure, chronic obstructive pulmonary disease, asthma or congestive heart failure. At an average length of stay of 11 days and a cost of $5,000 per patient, the total cost to provide ventilation each year $2.2 billion. The cost of lengthy ICU stays due to ventilator-induced complications is even greater—driving the total ICU costs into the tens of thousands of dollars per patient (12).

7.12.5 HOSPITAL ECONOMICS

At a price of $4,000, the Hattler Catheter will reduce costs to the hospital, as well as reducing ICU stays by up to half the time. The combination of lower device cost, plus reduced ICU time could result in savings of up to $15,000–$25,000 per patient. At the same time, because the reimbursement rate for a large organ catheter is higher than that for a ventilator, hospitals stand to increase revenues through the use of the Hattler Catheter (12).

7.12.6 GROWTH PROSPECTS

There are more than 10,000 ICUs worldwide. The larger ones maintain an average monthly patient load of about 20. A-Lung Company plans to penetrate 300 ICUs worldwide by 2009, treating an average of ten patients per month, which would generate sales of $109 million, three years after product launch in the United States. During the same period, employment is projected to increase from the current 10 full-time and five part-time employees to 15–20 full-time employees in 2005 and 300 in 2009 (12).

7.12.7 MANAGEMENT AND ADVISORS

The critical care in developing the Hattler Catheter has carried through to development of its management and product development team, board of directors and medical advisory board. The founders recruited Nick Kuhn, a bioscience executive from San Diego with extensive experience in the respiratory care market, to lead the company. Kuhn says the medical advisory board represents 'the top people in the field from key critical care centers across the U.S.'

"The more start-ups I'm involved in, the more I realize just how important the people are," Kuhn says. "Our management team and board are all seasoned people who have done this before. They've manufactured sterile medical devices, they've taken companies through clinical trials, they've raised money in the public markets."

As the company continues its quest to pull the plug on mechanical ventilators and the suffering they can impose, hundreds of thousands of patients around the world will continue to hold their breath, a task that ALung hopes to make a little easier (12).

7.12.8 FEASIBILITY OF A PUMPLESS EXTRACORPOREAL RESPIRATORY ASSIST DEVICE

University of Pittsburgh – Medical Center is evaluaty the efficacy and feasibility of a pumpless respiratory assist device for its capacity for carbon dioxide removal. In

five adult pigs the left femoral vein and artery were cannulated with a 20F cannula and connected to a low-pressure hollow-fiber artificial lung. After obtaining baseline values of mean arterial pressure, cardiac output, and blood flow across the artificial lung, the mean arterial pressure was reduced 20% and 40% relative to baseline; in a second phase, it was raised 20% and 40%. Cardiac output and artificial lung flow was simultaneously recorded. The carbon dioxide removal capacity of the artificial lung was determined by gradually increasing the arterial partial carbon dioxide tension of the animal.

An increase of 10 mm Hg in mean arterial pressure resulted in an increase of flow of 0.14 L/min. The mean pressure drop across the artificial lung was measured at 17–9 mm Hg. The shunt flow over the artificial lung varied between 14 and 25% of the cardiac output of the animal. Depending on inlet conditions, carbon dioxide removal by the artificial lung was between 62–22 mL/L/min and 104–25 mL/L/min.

A pumpless respiratory assist device can remove a significant proportion of the metabolic carbon dioxide production. However, adequate mean arterial pressure is mandatory to maintain sufficient flow across the device. The technique seems attractive because of its simplicity and can be used in acute lung injury in conjunction of apneic oxygenation for prolonged respiratory support (10). Figure 38 shows an implantable artificial lung.

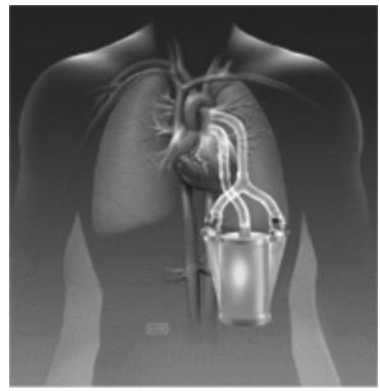


FIGURE 38 Schematic representation of the implantable artificial lung – MC3 pulmonary assist device (16).

7.12.9 DEVELOPMENT OF CARDIOPULMONARY BYPASS SYSTEM FOR LONG-TERM USE

Researches at University of Pittsburgh are also investing the possibility of and develop therapeutic options of cardiopulmonary support with a heart-lung assist device, such as percutaneous cardiopulmonary support and extracorporeal membrane oxygenation in treating patients with life-threatening circulatory and/or respiratory failure.

An integrated artificial heart-lung device has been developed as a long-term cardiopulmonary support system in respect of antithrombogenecity and durability. In particular, integration of a blood pump and artificial lung, employment of a special hollow fiber membrane, and heparin bonding surface treatment displaying excellent throm-

boresistance, provides several advantages including the marked reduction in the size of the apparatus and the preservation of the gas exchange function within a sufficient level. The possibility of therapeutic options has been investigated from the viewpoint of native lung metabolism (10).

7.12.10 MC3 PULMONARY ASSIST DEVICE COMPANY: BACKGROUND AND MISSION

MC3 is a Research and Development Company with over 10 years experience developing technologies to treat cardiopulmonary disease. MC3 develops novel ideas from conception through to the prototype and testing stages. MC3 performs contract device testing for medical device companies, and collaborates with academicians to develop ideas from the university setting to marketable product.

MC3 has four core technologies under patent protection: BioLung®, a pulmonary assist device (Fig. 35) to bridge patients to lung transplantation or recovery; Nitric oxide generating materials to enhance biocompatibility of blood contact surfaces, such as vascular grafts and stents; M-Pump, a novel roller pump with inherent pressure limitations and proprietary control strategies for automatic control of a heart/lung machine to regulate patient gas exchange (16).

MC3 plans to significantly increase its efforts surrounding nitric oxide generating materials. Research with these materials has shown potential benefits for use in stents, prosthetic vascular grafts, and several other medical devices.

7.13 CONCLUSIONS

In this chapter, the biomechanics of an artificial lung is presented. We know that the future of artificial lung systems will rely on the development of advance new materials. We believe that the development of artificial lung systems using live tissues is difficult due to the complexity and the complication of dealing with live tissue instead of just inert materials. As long as medicine keeps developing smaller artificial lung design and more plasma like solutions, the future seems full of hope and we expect that in the future, a fully functional lung system eill be available.

7.14 SUMMARY

Many diseases affect the respiratory system and may cause lung failure. With this in mind and the lack of lung donors, researchers and scientists have developed devices that can replace the natural lung. So far they have only developed temporary devices. These either assist the respiratory system during an operation or afterwards and can only be used for a short period of time. Here, we shall discuss the functioning, performance and, principle of operation of the artificial lungs. Respiratory assist devices, partially or totally, perform the function of the lungs. Besides the common usage in Cardiopulmonary Bypass procedures, auxiliary lungs could play a role in palliative treatment of wet-lung syndrome following shock, hyaline membrane disease, and organ transplant procedures. No one unit or even one design would be suitable for all cases. The multiplicity of applications undoubtedly would require a variety of units. Respiratory assist devices should perform its function without traumatizing the blood and should be efficient, reliable, safe, inexpensive, and easy to use. In addition, some

gross design features might include low priming volume, low head loss, and minimum surface area. The function of the artificial lung is to supply oxygen as well as to remove carbon dioxide. Artificial lungs, used in clinical cardiopulmonary bypass, are traditionally referred to as blood oxygenators, bubble oxygenators, disk oxygenators, or membrane oxygenators.

KEYWORDS

- **Active sing**
- **Advancing front theory**
- **Alveoli**
- **Alveolar epithelial cell**
- **Alveolar fluid**
- **Annular conduit**
- **Apical surface**
- **Arterialization**
- **Artificial lung**
- **Axial flow**
- **Basal surface**
- **Basement membrane material**
- **Blood borne**
- **Blood oxygenator**
- **Boundary layer**
- **Bubble membrane**
- **Bubble oxygenator**
- **Bypass surgery**
- **CABG**
- **Cardiopulmonary bypass**
- **CPB**
- **Carotid artery**
- **Catheter**
- **Congenital diaphragmatic hernia**
- **Continuous positive airway pressure**
- **Coronary artery bypass graft**
- **Dead space**
- **Diffusion**
- **Diffusivity**
- **Disk membrane**

- **Drive and control console**
- **ECMO**
- **Electrolyte**
- **Endothelial cell layer a human**
- **Epithelial cell layer**
- **Expiration**
- **Extracorporeal**
- **Extracorporeal circulation**
- **Extracorporeal membrane oxygenator**
- **Fiber membranes**
- **Film oxygenator**
- **Fluid limited case**
- **Functional residual capacity**
- **Heart lung bypass**
- **Heart lung machine**
- **Hemodilution**
- **Hemolysis**
- **Hemodiaysis access**
- **Hollow fiber**
- **IABP**
- **I:E ratio**
- **I:E ratio – expiratory interval to inspiratory period ratio**
- **IMO**
- **Intra aortic balloon pump**
- **Intravenous membrane oxygenator**
- **Inspiration**
- **Laminar flow**
- **Lung**
- **Mandatory mode**
- **Meconium aspiration syndrome**
- **Membrane limited case**
- **Membrane lung**
- **Membrane oxygenator**
- **Metabolism**
- **Neointimal hyperplasia**

- **Oscilloscope**
- **Oxygenation**
- **Oxygenation boundary layer**
- **Patient circuit**
- **Plasmatic**
- **Passive sing**
- **Pannus**
- **Partial pressure**
- **Perfusion**
- **Perfusionist**
- **Pleura**
- **Pneumatic**
- **Pneumatic delivery system**
- **Pneumotach**
- **Positive end expiratory pressure**
- **Pressure controlled ventilation**
- **Pressure support**
- **Pressure support level**
- **Priming volume**
- **Pulmonary circulation**
- **Pulmonary pathogen**
- **Pulmonary hypertension**
- **Pump oxygenator**
- **Pulsation rate membranous structure**
- **Respiratory assist device**
- **Respiratory quotient**
- **Respiratory system**
- **Spontaneous mode**
- **Secondary flow**
- **Solenoid valve**
- **Stenosis**
- **Thermal conductivity**
- **Total body perfusion**
- **Tubular conduit**
- **Vascular graft**

- **Vascular reconstruction**
- **Vena cava**
- **Ventilation**
- **Volume controlled ventilation**

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CHAPTER 8

BIOMECHANICS OF ARTIFICIAL KIDNEY[1,2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Ayeisha Correa, Beatriz Rutzen, and Arlene Santiago) for the course on Fluid Mechanics, INGE 4015. Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com> or visit at: http://www.ece.uprm.edu/~m_goyal/home.htm._We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2] The numbers in parentheses refer to cited references in the bibliography.

8.1 INTRODUCTION

The human kidney system consists of two kidneys, each about the size of an adult fist. They are located on either side of the spine just below the rib cage (Fig. 1). Our kidneys perform many complex and vital functions that keep us in good health. The kidney system works in conjunction with renal system to filter and dispose wastes of our body. If the kidney system fails then the patient has the option of a dialysis treatment (an artificial kidney) to carry out the vital functions. There are two different types: peritoneal dialysis, and hemodialysis. This chapter discusses functions and biomechanics of the human kidney system and the artificial kidney.

8.2 BIOMECHANICS OF THE HUMAN KIDNEY SYSTEM

8.2.1 DESCRIPTION OF THE HUMAN KIDNEY

The **kidneys** (Latin rēnēs, "kidney") are organs that serve several essential regulatory roles in most animals, including vertebrates and some invertebrates. They are essential in the urinary system and also serve homeostatic functions such as the regulation of electrolytes, maintenance of acid–base balance, and regulation of blood pressure (via maintaining salt and water balance). They serve the body as a natural filter of the blood, and remove wastes, which are diverted to the urinary bladder. In producing urine, the kidneys excrete wastes such as urea and ammonium, and they are also responsible for the reabsorption of water, glucose, and amino acids. The kidneys also produce hormones including calcitriol, erythropoietin, and the enzyme renin.

Located at the rear of the abdominal cavity in the retroperitoneum, the kidneys receive blood from the paired renal arteries, and drain into the paired renal veins. In humans the kidneys are located in the abdominal cavity, more specifically in the paravertebral gutter and lie in a retroperitoneal position at a slightly oblique angle (Figs. 1 and 2). There are two, one on each side of the spine. The asymmetry within the abdominal cavity caused by the liver typically results in the right kidney being slightly lower than the left, and left kidney being located slightly more medial than the right. The left kidney is approximately at the vertebral level T12 to L3, and the right slightly lower. The right kidney sits just below the diaphragm and posterior to the liver, the left below the diaphragm and posterior to the spleen. Resting on top of each kidney is an adrenal gland. The upper (cranial) parts of the kidneys are partially protected by the 11th and twelfth ribs, and each whole kidney and adrenal gland are surrounded by two layers of fat (the perirenal and pararenal fat) and the renal fascia. Each adult kidney weighs between 125 and 170 grams in males and between 115 and 155 grams in females. The left kidney is typically slightly larger than the right kidney.

The kidney has a bean-shaped structure; each kidney has a convex and concave surface. The concave surface, the renal hilum, is the point at which the renal artery enters the organ, and the renal vein and ureter leave. The kidney is surrounded by tough fibrous tissue, the renal capsule, which is itself surrounded by perinephric fat, renal fascia (of Gerota) and paranephric fat. The anterior (front) border of these tissues is the peritoneum, while the posterior (rear) border is the transversalis fascia. The superior border of the right kidney is adjacent to the liver; and the spleen, for the

left kidney. Therefore, both move down on inhalation. The kidney is approximately 11–14 cm in length, 6 cm wide and 4 cm thick.

The substance, or parenchyma, of the kidney is divided into two major structures: superficial is the renal cortex and deep is the renal medulla. Grossly, these structures take the shape of 8 to 18 cone-shaped renal lobes, each containing renal cortex surrounding a portion of medulla called a renal pyramid (of Malpighi). Between the renal pyramids are projections of cortex called renal columns (of Bertin). Nephrons, the urine-producing functional structures of the kidney, span the cortex and medulla. The initial filtering portion of a nephron is the renal corpuscle, located in the cortex, which is followed by a renal tubule that passes from the cortex deep into the medullary pyramids. Part of the renal cortex, a medullary ray is a collection of renal tubules that drain into a single collecting duct.

The tip, or papilla, of each pyramid empties urine into a minor calyx; minor calyces empty into major calyces, and major calyces empty into the renal pelvis, which becomes the ureter. At the hilum, the ureter and renal vein exit the kidney while the renal artery enters. Surrounding these structures is hilar fat and lymphatic tissue with lymph nodes. The hilar fat is contiguous with a fat-filled cavity called the renal sinus. The renal sinus collectively contains the renal pelvis and calyces and separates these structures from the renal medullary tissue.

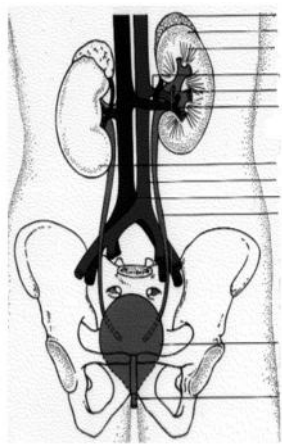

FIGURE 1 The human kidney system (20).

Renal histology studies the structure of the kidney as viewed under a microscope. Various distinct cell types in the kidney are: Kidney glomerulus parietal cell, kidney glomerulus podocyte, kidney proximal tubule brush border cell, loop of Henle thin segment cell, thick ascending limb cell, kidney distal tubule cell, kidney collecting duct cell, interstitial kidney cells, and renal arteries and their branches.

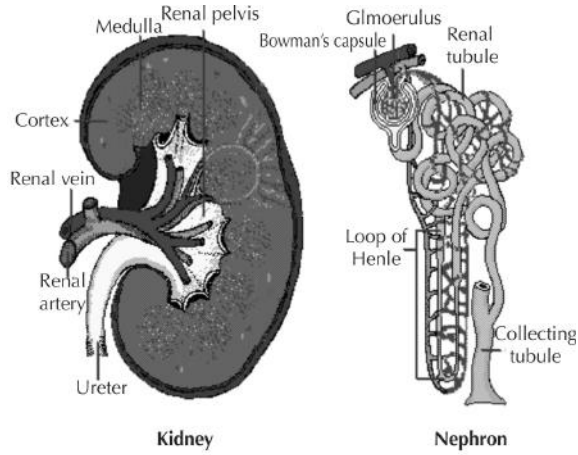

FIGURE 2 Kidney and nephron (20).

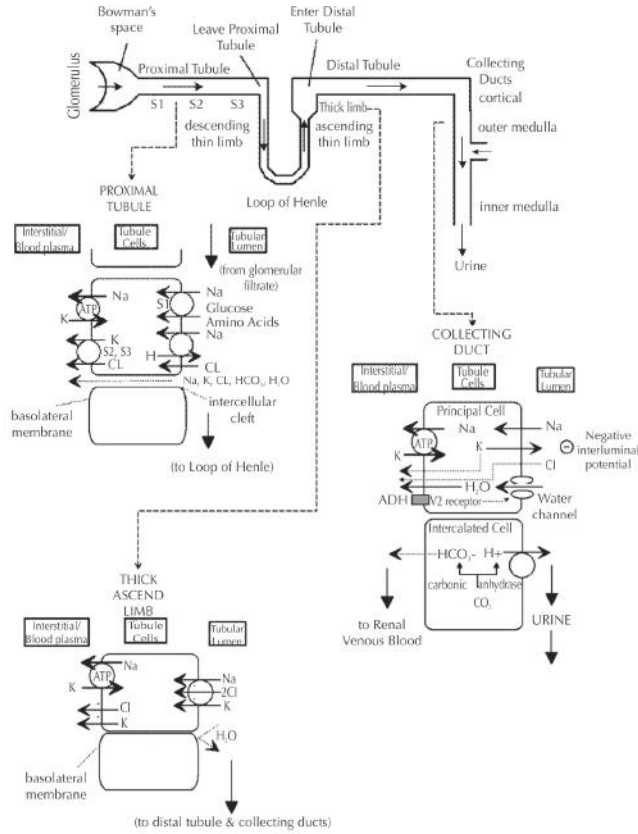

FIGURE 3 The normal renal physiology showing where some types of diuretics act, and what they do.

The renal artery enters into the kidney at the level of first lumbar vertebra just below the superior mesenteric artery. As it enters the kidney it divides into branches: first the segmental artery, which divides into 2 or 3 lobar arteries, then further divides into interlobar arteries, which further divide into the arcuate artery which leads into the interlobular artery, which form afferent arterioles. The afferent arterioles form the glomerulus (network of capillaries closed in Bowman's capsule). From here, efferent arterioles leaves the glomerulus and divide into peritubular capillaries, which drain into the interlobular veins and then into arcuate vein and then into interlobar vein, which runs into lobar vein, which opens into the segmental vein and which drains into the renal vein, and then from it blood moves into the inferior vena cava.

8.2.2 BLOOD SUPPLY

The kidneys receive blood from the renal arteries, left and right, which branch directly from the abdominal aorta. Despite their relatively small size, the kidneys receive approximately 20% of the cardiac output. Each renal artery branches into segmental arteries, dividing further into interlobar arteries, which penetrate the renal capsule and extend through the renal columns between the renal pyramids. The interlobar arteries then supply blood to the arcuate arteries that run through the boundary of the cortex and the medulla. Each arcuate artery supplies several interlobular arteries that feed into the afferent arterioles that supply the glomeruli.

The interstitum (or interstitium) is the functional space in the kidney beneath the individual filters (glomeruli), which are rich in blood vessels. The interstitum absorbs fluid recovered from urine. Various conditions can lead to scarring and congestion of this area, which can cause kidney dysfunction and failure.

After filtration process, the blood moves through a small network of venules that converge into interlobular veins. As with the arteriole distribution the veins follow the same pattern, the interlobular provide blood to the arcuate veins then back to the interlobar veins, which come to form the renal vein exiting the kidney for transfusion for blood.

8.2.3 INNERVATION

The kidney and nervous system communicate via the renal plexus, whose fibers course along the renal arteries to reach each kidney. Input from the sympathetic nervous system triggers vasoconstriction in the kidney, thereby reducing renal blood flow. The kidney also receives input from the parasympathetic nervous system, by way of the renal branches of the vagus nerve (cranial nerve X); the function of this is yet unclear. Sensory input from the kidney travels to the T10–11 levels of the spinal cord and is sensed in the corresponding dermatome. Thus, pain in the flank region may be referred from corresponding kidney.

8.2.4 RENAL PHYSIOLOGY: FUNCTIONS OF THE KIDNEY

Renal physiology is the study of all functions of the kidney, including reabsorption of glucose, amino acids, and other small molecules; regulation of sodium, potassium, and other electrolytes; regulation of fluid balance and blood pressure; maintenance of acid-base balance; the production of various hormones including erythropoietin,

and the activation of vitamin D (See Fig. 3). Much of renal physiology is studied at the level of the nephron, the smallest functional unit of the kidney (Fig. 2). Each nephron begins with a filtration component that filters blood entering the kidney. This filtrate then flows along the length of the nephron, which is a tubular structure lined by a single layer of specialized cells and surrounded by capillaries. The major functions of these lining cells are the reabsorption of water and small molecules from the filtrate into the blood, and the secretion of wastes from the blood into the urine.

Proper function of the kidney requires that it receives and adequately filters blood. This is performed at the microscopic level by many hundreds of thousands of filtration units called renal corpuscles, each of which is composed of a glomerulus and a Bowman's capsule. A global assessment of renal function is often ascertained by estimating the rate of filtration, called the glomerular filtration rate (GFR). Every day, the kidneys process about 200 quarts (One US quart = 32 fluid ounces = 946.35295 mL) of blood and filter out about 2 quarts of waste products and extra water. The waste and extra water turns into urine that flows to the bladder through tubes called ureters.

The functions of the kidney can be divided into three groups: secretion of hormones, gluconeogenesis, and extracellular homeostasis of pH and blood components. The nephron is the functional unit of the kidney.

8.2.4.1 SECRETION OF HORMONES

The kidneys secrete a variety of hormones, including erythropoietin, and the enzyme renin. Erythropoietin is released in response to hypoxia (low levels of oxygen at tissue level) in the renal circulation. It stimulates erythropoiesis (production of red blood cells) in the bone marrow. Calcitriol, the activated form of vitamin D, promotes intestinal absorption of calcium and the renal reabsorption of phosphate. Part of the renin-angiotensin-aldosterone system, renin is an enzyme involved in the regulation of aldosterone levels.

8.2.4.2 GLUCONEOGENESIS

The kidney in humans is capable of producing glucose from lactate, glycerol and glutamine. The kidney is responsible for about half of the total gluconeogenesis in fasting humans. The regulation of glucose production in the kidney is achieved by action of insulin, catecholamines and other hormones. Renal gluconeogenesis takes place in the renal cortex. The renal medulla is incapable of producing glucose due to absence of necessary enzymes.

8.2.4.3 EXTRACELLULAR HOMEOSTASIS

The kidney is responsible for maintaining a balance of the following substances:

Substance	Proximal tubule	Loop of Henle	Distal tubule	Collecting duct
If **glucose** is not reabsorbed by the kidney, it appears in the urine, in a condition known as glycosuria. This is associated with diabetes mellitus.	Reabsorption (almost 100%) via sodium-glucose transport proteins (apical) and GLUT (basolateral).	–	–	–

Substance	Proximal tubule	Loop of Henle	Distal tubule	Collecting duct
Oligopeptides, proteins, and amino acids are reabsorbed nearly completely.	Reabsorption	–	–	–
Urea: Regulation of osmolality. Varies with ADH.	Reabsorption (50%) via passive transport.	Secretion	–	Reabsorption in medullary collecting ducts.
Sodium: Uses Na-H antiporter, Na-glucose symporter, sodium ion channels (minor).	Reabsorption (65%, isosmotic).	Reabsorption (25%, thick ascending, Na-K-2Cl symporter).	Reabsorption (5%, sodium-chloride symporter).	Reabsorption (5%, principal cells), stimulated by aldosterone via ENaC.
Chloride: Usually follows sodium. Active (transcellular) and passive (paracellular).	Reabsorption.	Reabsorption (thin ascending, thick ascending, Na-K-2Cl symporter).	Reabsorption (sodium-chloride symporter).	–
Water: Uses aquaporin water channels. See also diuretic.	Absorbed osmotically along with solutes.	Reabsorption (descending).	–	Reabsorption (regulated by ADH, via arginine vasopressin receptor 2)
Bicarbonate: Helps maintain acid-base balance.	Reabsorption (80–90%).	Reabsorption (thick ascending).	–	Reabsorption (intercalated cells, via band 3 and pendrin).
Protons: Uses vacuolar H+ATPase.	–	–	–	Secretion (intercalated cells).
Potassium: Varies upon dietary needs.	Reabsorption (65%).	Reabsorption (20%, thick ascending, Na-K-2Cl symporter).	–	Secretion (common, via Na+/K+-ATPase, increased by aldosterone), or reabsorption (rare, hydrogen potassium ATPase).

Substance	Proximal tubule	Loop of Henle	Distal tubule	Collecting duct
Calcium: Uses calcium ATPase, sodium-calcium exchanger.	Reabsorption.	Reabsorption (thick ascending) via passive transport.	–	–
Magnesium: Ca and Mg compete, and an excess of one can lead to excretion of the other.	Reabsorption.	Reabsorption (thick ascending).	Reabsorption.	–
Phosphate: Excreted as titratable acid..	Reabsorption (85%) via sodium/phosphate cotransporter. Inhibited by parathyroid hormone.	–	–	–
Carboxylate.	Reabsorption (100%) via carboxylate transporters.	–	–	–

Our body is very sensitive to its pH. Outside the range of pH that is compatible with life, proteins are denatured and digested, enzymes lose their ability to function, and the body is unable to sustain itself. The kidneys maintain acid-base homeostasis by regulating the pH of the blood plasma. Gains and losses of acid and base must be balanced. Acids are divided into "volatile acids" and "nonvolatile acids."

The major homeostatic control point for maintaining this stable balance is **renal excretion**. The kidney is directed to excrete or retain sodium via the action of aldosterone, antidiuretic hormone (ADH, or vasopressin), atrial natriuretic peptide (ANP), and other hormones. Abnormal ranges of the fractional excretion of sodium can imply acute tubular necrosis or glomerular dysfunction.

8.2.5 MECHANISMS OF RENAL SECRETION (FIG. 4)

The ability of the kidney to perform many of its functions depends on the three fundamental functions of filtration, reabsorption, and secretion, whose sum is renal excretion:

$$\text{Urinary excretion rate} = \text{Filtration rate} - \text{Reabsorption rate} + \text{Secretion rate} \quad (1)$$

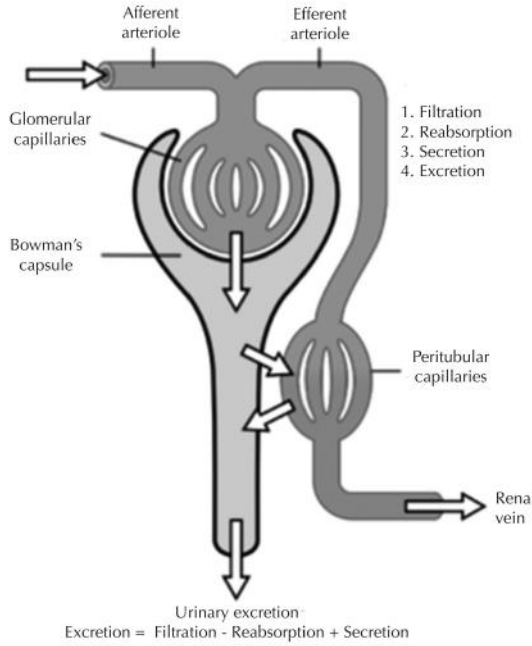

FIGURE 4 Basic physiologic mechanisms of the kidney.

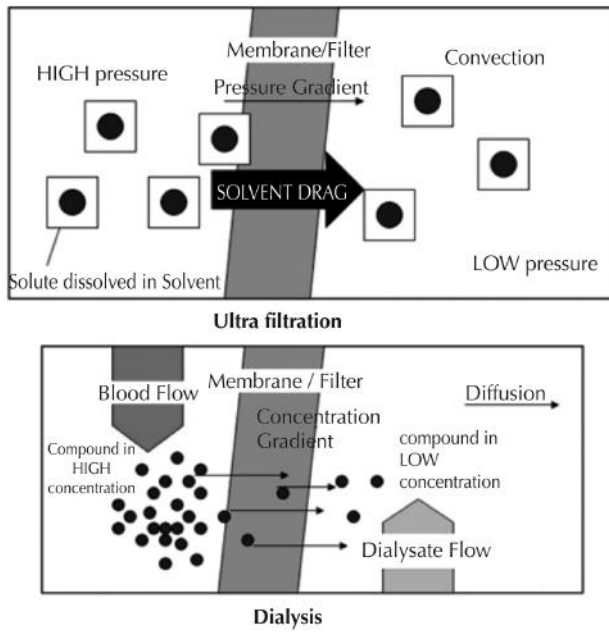

FIGURE 5 Ultrafiltration (top) and dialysis (bottom).

8.2.5.1 FILTRATION

The blood is filtered by nephrons, the functional units of the kidney. Cells, proteins, and other large molecules are filtered out of the glomerulus by a process of ultrafiltration, leaving an ultrafiltrate that resembles plasma (except that the ultrafiltrate has negligible plasma proteins) to enter Bowman's space. Filtration is driven by Starling forces. The ultrafiltrate is passed through, in turn, the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule, and a series of collecting ducts to form urine. In biological terms, **ultrafiltration** occurs at the barrier between the blood and the filtrate in the renal corpuscle or Bowman's capsule in the kidneys. The Bowman's capsule contains a dense capillary network called the glomerulus. Blood flows into these capillaries through the afferent arteriole and leaves through the efferent arteriole. The blood pressure in the afferent arteriole is higher than the blood pressure in the efferent arteriole. This is because the efferent arteriole has a smaller diameter than the afferent arteriole. The high hydrostatic pressure forces small molecules such as water, glucose, amino acids, sodium chloride and urea through the filter, from the blood in the glomerular capsule across the basement membrane of the Bowman's capsule and into the nephron. This process is called ultrafiltration. The fluid filtered in this way is called glomerular filtrate. Glomerular pressure is about 75 millimeters of mercury (10 kPa). It is opposed by osmotic pressure (30 mmHg, 4.0 kPa) and hydrostatic pressure (20 mmHg, 2.7 kPa) of solutes present in capsular space. This difference in pressure is called effective pressure (25 mmHg, 3.3 kPa). It is also used in hemodialysis to clean whole blood while keeping its composition intact. The structures of the layers of the glomerulus determine their **permeability-selectivity** (permselectivity). For instance, small ions such as sodium and potassium pass freely, while larger plasma proteins, such as hemoglobin and albumin have practically no permeability at all. Also, negatively charged molecules will pass through far less frequently than positively charged ones. **Slow Continuous Ultrafiltration (SCUF)** is an artificial method which approximately mimics the ultrafiltration function of the kidneys. SCUF is a continuous renal replacement therapy (CRRT) generally used to remove fluid from fluid overloaded patients suffering acute renal failure. During SCUF blood is removed from the body and is passed through an extracorporeal circuit through a hemofilter and a predetermined percentage of plasma water is removed based upon a prescription. Typically, no more than 2 liters per hour of fluid is removed. The remaining blood is returned to the patient. Unlike hemodialysis, hemofiltration and hemodiafiltration, no dialysate or replacement fluids are used in SCUF.

8.2.5.2 REABSORPTION

Tubular reabsorption is a process by which solutes and water are removed from the tubular fluid and transported into the blood. It is called reabsorption (and not absorption) because these substances have already been absorbed once (particularly in the intestines). Reabsorption is a two-step process beginning with the active or passive extraction of substances from the tubule fluid into the renal interstitium (the connective tissue that surrounds the nephrons), and then the transport of these substances from the interstitium into the bloodstream. These transport processes are driven by Starling forces, diffusion, and active transport.

The *Starling equation* illustrates the role of hydrostatic and oncotic forces (the so-called Starling forces) in the movement of fluid across capillary membranes (Fig. 6). Capillary fluid movement may occur as a result of three processes: diffusion, filtration and pinocytosis. Starling's equation refers to fluid movement across the capillary membrane that occurs as a result of filtration (Fig. 6). In the glomerular capillaries, there is a net fluid filtration of 125 mL/min (about 180 liters/day). In the rest of the body's capillaries, there is a total net transcapillary fluid movement of 20 mL/min (about 28.8 liters/day) as a result of filtration. This is several orders of magnitude lower than the total diffusional water flux at the capillary membrane, as that is about 80,000 liters per day. The Starling equation was formulated in 1896 by the British physiologist Ernest Starling, also known for the Frank–Starling law of the heart.

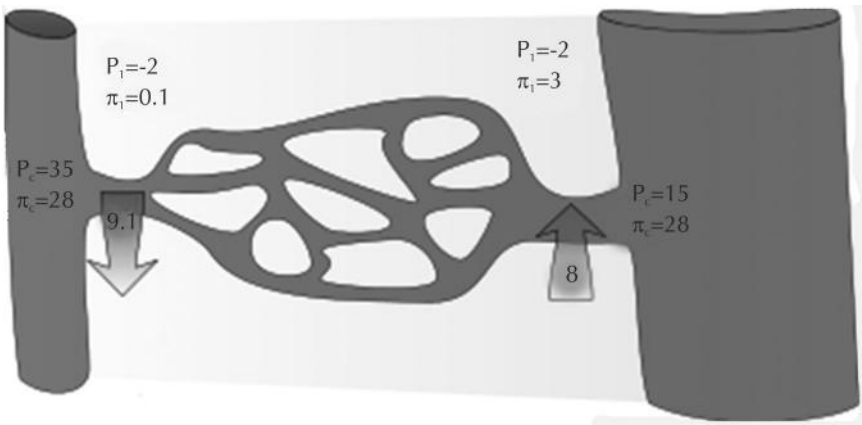

FIGURE 6 The Startling model. Note that the concentration of interstitial solutes (orange) increases proportionally to the distance from the arteriole.

The Starling equation:

$$Jv = K_f((P_c - P_i) - \sigma * (\pi_c - \pi_i)) \quad (2)$$

where: J_v = the net fluid movement between compartments or GFR = dQ/dt.
$((P_c - P_i) - \sigma * (\pi_c - \pi_i))$ = the net driving force.
P_c is the capillary hydrostatic pressure
P_i is the interstitial hydrostatic pressure
π_c is the capillary oncotic pressure
π_i is the interstitial oncotic pressure
K_f is the filtration coefficient = a proportionality constant
σ is the reflection coefficient

In Eq. (2): By convention, outward force is defined as positive and inward force is defined as negative. The solution to the equation is known as the net filtration or net fluid movement (J_v). If positive, fluid will tend to leave the capillary (filtration). If negative, fluid will tend to enter the capillary (absorption). This equation has a number of important physiologic implications, especially when pathologic processes grossly

alter one or more of the variables. Note that previously it was believed that at steady state the arterial capillaries filter fluid and the venous capillaries reabsorb it, as shown in Fig. 6. Though many physiology textbooks still use this misconception, modern evidence shows that in most cases venular blood pressure exceeds the opposing pressure, thus maintaining a positive outward force. This indicates that capillaries are normally in a state of filtration along their entire length. Pressures are often measured in millimeters of mercury (mmHg), and the filtration coefficient in milliliters per minute per millimeter of mercury (mL/min/mmHg). Therefore, the Eq. (2) implies that the net filtration (Jv) is proportional to the net driving force. The four variables on the right hand side of equation 2/are called **Starling forces** that contribute to the net driving force. In Eq. (2), K_f is a constant of proportionality and is defined as filtration coefficient that is a product of capillary surface area and capillary hydraulic conductance. The high value of K_f indicates a highly water permeable capillary. A low value of K_f indicates a low capillary permeability. The **reflection coefficient** in Eq. (2) is often thought of as a correction factor that varies from 0 to 1. Glomerular capillaries have a reflection coefficient close to 1 as normally no protein crosses into the glomerular filtrate. In contrast, hepatic sinusoids have a low reflection coefficient (generally <1) as they are quite permeable to protein. This is advantageous because albumin is produced in hepatocytes and can relatively freely pass from these cells into the blood in the sinusoids. The predominant pathway for albumin and other proteins to enter the circulation is via the lymph. The K_f is based on the concept: The difference in oncotic pressures contributes to the net driving force because most capillaries in the body are fairly impermeable to the large molecular weight proteins. (The term ultrafiltration is usually used to refer to this situation where the large molecules are retained by a semipermeable membrane but water and low molecular weight solutes can pass through the membrane). Many body capillaries do have a small permeability to proteins (such as albumins). This small protein leakage has two important effects: 1. The interstitial fluid oncotic pressure is higher than it would otherwise be in that tissue; 2. Not all of the protein present is effective in retaining water so the effective capillary oncotic pressure is lower than the measured capillary oncotic pressure. Both these effects decrease the contribution of the oncotic pressure gradient to the net driving force. The reflection coefficient (σ) is used to correct the magnitude of the measured gradient to 'correct for' the ineffectiveness of some of the oncotic pressure gradient. Approximate values for the variables in Eq. (2) for both arterioles and venules are tabulated below:

Location	**P_c (mmHg)**	**P_i (mmHg)**	**$\sigma\pi_c$ (mmHg)**	**$\sigma\pi_i$ (mmHg)**
Arteriolar end of capillary	+35	−2	+28	+0.1
Venular end of capillary	+15	−2	+28	+3

Some albumin escapes from the capillaries and enters the interstitial fluid where it would produce a flow of water equivalent to that produced by a hydrostatic pressure of +3 mmHg. Thus, the difference in protein concentration would produce a flow of fluid into the vessel at the venous end equivalent to 28 − 3 = 25 mmHg of hydrostatic pressure. The total oncotic pressure present at the venous end could be considered as +25 mmHg. In the beginning (arteriolar end) of a capillary, there is a net driving

force on the right hand side of Eq. (2) outwards from the capillary of +9 mmHg. In the end (venular end), on the other hand, there is a net driving force of −8 mmHg. Assuming that the net driving force declines linearly, then there is a mean net driving force outwards from the capillary as a whole, which also results in that more fluid exits a capillary than reenters it. The lymphatic system drains this excess fluid. The Eq. (2) is very useful for explaining physiological phenomena happening at the capillary (e.g., the formation of edemas), but has very limited clinical usefulness. Mostly this reflects the impossibility of easily measuring all six variables together in actual patients.

8.2.5.3 INDIRECT REABSORPTION

In some cases, reabsorption is indirect. For example, bicarbonate (HCO^{-3}) does not have a transporter, so its reabsorption involves a series of reactions in the tubule lumen and tubular epithelium. It begins with the active secretion of a hydrogen ion (H^+) into the tubule fluid via a Na/H exchanger: In the lumen, the H^+ combines with HCO^{-3} to form carbonic acid (H_2CO_3). Luminal carbonic anhydrase enzymatically converts H_2CO_3 into H_2O and CO_2. The CO_2 freely diffuses into the cell**.** In the epithelial cell, cytoplasmic carbonic anhydrase converts the CO_2 and H_2O (which is abundant in the cell) into H_2CO_3. The H_2CO_3 readily dissociates into H^+ and HCO^{3-}. The HCO^{3-} is facilitated out of basolateral membrane of the cell. Some key regulatory hormones for reabsorption include: aldosterone, which stimulates active sodium reabsorption (and water as a result); antidiuretic hormone, which stimulates passive water reabsorption**.** Both hormones exert their effects principally on the collecting ducts.

8.2.5.4 SECRETION

Tubular secretion is the transfer of materials from peritubular capillaries to renal tubular lumen. Tubular secretion is caused mainly by active transport. Usually only a few substances are secreted. These substances are present in great excess, or are natural poisons. Many drugs are eliminated by tubular secretion.

8.2.6 BIOFLUID DYNAMICS OF RENAL FUNCTION

Renal function, in nephrology, is an indication of the state of the kidney and its role in renal physiology. A simple means of estimating renal function is to measure pH, blood urea nitrogen, creatinine, and basic electrolytes (including sodium, potassium, chloride, and bicarbonate). As the kidney is the most important organ in controlling these values, any derangement in these values may suggest renal impairment.

Glomerular filtration rate (GFR, Eq. (2)) describes the flow rate of filtered fluid through the kidney. Creatinine clearance rate (CCr or CrCl) is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. Creatinine clearance exceeds GFR due to creatinine secretion, which can be blocked by cimetidine. In alternative fashion, overestimation by older serum creatinine methods resulted in an underestimation of creatinine clearance, which provided a less biased estimate of GFR. Both GFR and CCr may be accurately calculated by comparative measurements of substances in the blood and urine, or estimated by formulas using just a blood test result (eGFR and eCCr). The results of these tests are important in assessing the excretory function of the kidneys. For example, grading of chronic renal insufficiency and dosage of drugs that are excreted primarily via urine

are based on GFR (or creatinine clearance). It is commonly believed to be the amount of liquid filtered out of the blood that gets processed by the kidneys. In physiological terms, these quantities (volumetric blood flow and mass removal) are related only loosely.

8.2.6.1 GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR, mL/min/1.73 m^2) is the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time. Central to the physiologic maintenance of GFR is the differential basal tone of the afferent and efferent arterioles. The GFR is equal to the Clearance Rate when any solute is freely filtered and is neither reabsorbed nor secreted by the kidneys. The GFR is the quantity of the substance in the urine that originated from a calculable volume of blood. Relating this principle in Eq. (3) for the substance used, the product of urine concentration and urine flow equals the mass of substance excreted during the time that urine has been collected. This mass equals the mass filtered at the glomerulus as nothing is added or removed in the nephron. Dividing this mass by the plasma concentration gives the volume of plasma which the mass must have originally come from, and thus the volume of plasma fluid that has entered Bowman's capsule within the aforementioned period of time. The GFR is typically recorded in units of volume per time (mL/min).

$$\text{GFR} = (\text{Urine concentration } x \text{ urine flow})/(\text{Plasma concentration}) \quad (3)$$

The normal range of GFR, adjusted for body surface area, is 100–130 mL/min/1.73 m^2 in men and women. In children, GFR measured by inulin clearance is 110 mL/min/1.73 m^2 until 2 years of age in both sexes, and then it progressively decreases. After age 40, GFR decreases progressively with age, by about 0.4–1.2 mL/min per year. For most patients, a GFR over 60 mL/min/1.73 m^2 is adequate. But significant decline of the GFR from a previous test result can be an early indicator of kidney disease requiring medical intervention. The sooner kidney dysfunction is diagnosed and treated the greater odds of preserving remaining nephrons, and preventing the need for dialysis. The severity of chronic kidney disease (CKD) is described by following six stages based on the value of GFR in mL/min/1.73 m^2. The most severe three are defined by the MDRD-eGFR value, and first three also depend on whether there is other evidence of kidney disease (e.g., proteinuria). Some physicians add CKD5D for those stage 5 patients requiring dialysis; many patients in CKD5 are not yet on dialysis. Others add a "T" to patients who have had a transplant regardless of stage. Not all clinicians agree with the above classification, suggesting that it may mislabel patients with mildly reduced kidney function, especially the elderly, as having a disease. A conference was held in 2009 regarding these controversies by Kidney Disease: "Improving Global Outcomes (KDIGO) on CKD: Definition, Classification and Prognosis, gathering data on CKD prognosis to refine the definition and staging of CKD."

0 Normal kidney function – GFR > 90 and no proteinuria
1 CKD1 – GFR > 90 with evidence of kidney damage
2 CKD2 (Mild) – GFR = 60 to 89 with evidence of kidney damage
3 CKD3 (Moderate) – GFR = 30 to 59

4 CKD4 (Severe) – GFR = 15 to 29
5 CKD5 kidney failure – GFR < 15

There are several different techniques used to calculate or estimate the glomerular filtration rate (GFR or eGFR). The Eq. (3) is only for estimating GFR, when it is equal to the **Clearance Rate**. The GFR can be measured by injecting inulin or the inulin-analogon sinistrin into the plasma. Since both, inulin and sinsitrin, are neither reabsorbed nor secreted by the kidney after glomerular filtration, therefore their rate of excretion is directly proportional to the rate of filtration of water and solutes across the glomerular filter. Compared to the MDRD formula, the inulin clearance slightly overestimates the glomerular function. In early stage renal disease, the inulin clearance may remain normal due to hyperfiltration in the remaining nephrons. Incomplete urine collection is an important source of error in inulin clearance measurement. GFR is affected by the Starling forces as shown in Eq. (2) above. The filtration coefficient (K_f) in Eq. (2) is almost impossible to measure physically. However, it can be determined experimentally. Methods of determining the GFR are described above. Therefore, filtration coefficient can be found by dividing the experimental GFR by the net filtration pressure (defined in Eq. (2) above.

$$K_f = (\text{GFR})/(\text{Net filtration pressure}) = (\text{GFR})/(P_G - P_B - \pi_G + \pi_B) \tag{4}$$

The hydrostatic pressure (P_G) within the glomerular capillaries is determined by the pressure difference between the fluid entering immediately from the afferent arteriole and leaving through the efferent arteriole. The pressure difference is approximated by the product of the total resistance of the respective arteriole and the flux of blood through it:

$$(P_a - P_G) = R_a \, x \, Q_a, \text{ and } (P_G - P_e) = R_e \, x \, Q_e \tag{5}$$

where: $\boldsymbol{P_a}$ is the afferent arteriole pressure; $\boldsymbol{P_e}$ is the efferent arteriole pressure; $\boldsymbol{R_a}$ is the afferent arteriole resistance; $\boldsymbol{R_e}$ is the efferent arteriole resistance; $\boldsymbol{Q_a}$ is the afferent arteriole flux; and $\boldsymbol{Q_e}$ is the efferent arteriole flux. The pressure in the Bowman's capsule and proximal tubule is determined by the difference between the pressure in the Bowman's capsule ($\boldsymbol{P_B}$) and the descending tubule ($\boldsymbol{P_d}$):

$$P_B - P_d = R_d x \, (Q_a - Q_e) \tag{6}$$

where: $\boldsymbol{P_d}$ is the pressure in the descending tubule, and $\boldsymbol{R_d}$ is the resistance of the descending tubule. Blood plasma has a good number of proteins in it and they exert an inward directed force called the colloid osmotic pressure (π_G) on the water in hypotonic solutions across a membrane, i.e., in the Bowman's capsule. Because plasma proteins are virtually incapable of escaping the glomerular capillaries, this oncotic pressure is defined by the Ideal Gas Law:

$$\pi_G = \boldsymbol{R*T*c} \tag{7}$$

where: $\boldsymbol{R}$ is the universal gas constant, $\boldsymbol{T}$ is an absolute temperature, and $\boldsymbol{c}$ is concentration in mol per liter of plasma proteins (Note: the solutes can freely diffuse through the glomerular capsule). The value of π_B in Eq. (4) is almost always assumed to be zero because, in a healthy nephron, there should be no proteins in the Bowman's Capsule.

8.2.6.2 CREATININE-BASED APPROXIMATIONS OF GFR

In clinical practice, however, creatinine clearance or estimates of creatinine clearance based on the serum creatinine level are used to measure GFR. Creatinine is produced naturally by the body (creatinine is a breakdown product of creatine phosphate, which is found in muscle). It is freely filtered by the glomerulus, but also actively secreted by the peritubular capillaries in very small amounts such that creatinine clearance overestimates actual GFR by 10–20%. This margin of error is acceptable, considering the ease with which creatinine clearance is measured. Unlike precise GFR measurements involving constant infusions of inulin, creatinine is already at a steady-state concentration in the blood, and so measuring creatinine clearance is much less cumbersome. However, creatinine estimates of GFR have their limitations. All of the estimating equations depend on a prediction of the 24-hour creatinine excretion rate, which is a function of muscle mass. One of the equations, the Cockcroft and Gault equation does not correct for race, and it is known that black men and women have a higher amount of muscle mass than Caucasians; hence, they will have higher serum creatinine levels at any level of clearance.

A common mistake made when just looking at serum creatinine is the failure to account for muscle mass. Hence, an older woman with a serum creatinine of 1.4 mg/dL may actually have a moderately severe degree of renal insufficiency, whereas a young muscular male, in particular if black, can have a normal level of renal function at this serum creatinine level. Creatinine-based equations should be used with caution in cachectic patients and patients with cirrhosis. They often have very low muscle mass and a much lower creatinine excretion rate than predicted by the equations below, such that a cirrhotic patient with a serum creatinine of 0.9 mg/dL may have a moderately severe degree of renal insufficiency.

Creatinine Clearance, C_{Cr}: One method of determining GFR from creatinine is to collect urine (usually for 24 h) to determine the amount of creatinine that was removed from the blood over a given time interval. If one removes, say, 1440 mg in 24 hr, this is equivalent to removing 1 mg/min. If the blood concentration is 0.01 mg/mL (1 mg/dL), then one can say that 100 mL/min of blood is being "cleared" of creatinine, since, to get 1 mg of creatinine, 100 mL of blood containing 0.01 mg/mL would need to have been cleared. Creatinine clearance (C_{Cr}) is calculated from the creatinine concentration in the collected urine sample (U_{Cr}), urine flow rate (V), and the plasma concentration (P_{Cr}). Since the product of urine concentration and urine flow rate yields creatinine excretion rate, which is the rate of removal from the blood, creatinine clearance is calculated as removal rate per min ($U_{Cr} \times V$) divided by the plasma creatinine concentration (P_{Cr}). The procedure is summarized in Eq. (8):

$$C_{Cr} = (U_{Cr}\, x\, \mathrm{V})/(P_{Cr}) \tag{8}$$

Example: A person has a plasma creatinine concentration of 0.01 mg/ml and produces one mL of urine per minute with a creatinine concentration of 1.25 mg/ml. Calculate creatinine clearance using Eq. (8).

$C_{Cr} = (1.25 \times 1.0)/0.0.1 = 125$ mL/minute.

The common procedure involves undertaking a 24-hour urine collection, from empty-bladder one morning to the contents of the bladder the following morning, with

a comparative blood test for the morning. The urinary flow rate per minute is still calculated, hence:

$$C_{Cr} = (U_{Cr} \times 24\ hr\ volume)/(P_{Cr} \times 24 \times 60\ min) \tag{9}$$

To allow comparison of results between people of different sizes, the $\boldsymbol{C_{Cr}}$ is often corrected for the body surface area (*BSA*) and expressed compared to the average sized man as mL/min/1.73 m^2. While most adults have a *BSA* that approaches 1.7 (1.6 to 1.9), extremely obese or slim patients should have their C_{Cr} corrected for their actual *BSA*. The *BSA* can be calculated on the basis of weight and height as shown in Eqs. (11) to (15). A commonly used and simple one is the Mosteller formula.

$$C_{Cr\text{-}}CO_{rrected} = (U_{Cr} \times 1.73)/(\text{BSA}) \tag{10}$$

The Mosteller formula, BSA:

$$\text{BSA (m}^2\text{)} = ((\text{Height (cm)} \times \text{Weight (kg)})/3600)^{½} \tag{11}$$

The DuBois and DuBois formula:

$$\text{BSA (m}^2\text{)} = 0.20247 \times \text{Height (m)}^{0.725} \times \text{Weight (kg)}^{0.425} \tag{12}$$

The Haycock formula:

$$\text{BSA (m}^2\text{)} = 0.024265 \times \text{Height (cm)}^{0.3964} \times \text{Weight (kg)}^{0.5378} \tag{13}$$

The Gehan and George formula:

$$\text{BSA (m}^2\text{)} = 0.0235 \times \text{Height (cm)}^{0.42246} \times \text{Weight (kg)}^{0.51456} \tag{14}$$

The Boyd formula:

$$\text{BSA (m}^2\text{)} = 0.0003207 \times \text{Height (cm)}^{0.3} \times \text{Weight (grams)}^{(0.7285 - (0.0188 \times \text{LOG(grams)}))} \tag{15}$$

Twenty-four hour urine collection to assess creatinine clearance is no longer widely performed, due to difficulty in assuring complete specimen collection. To assess the adequacy of a complete collection, one always calculates the amount of creatinine excreted over a 24-hour period. This amount varies with muscle mass, and is higher in young people versus old, in blacks versus whites, and in men versus women. An unexpectedly low or high 24-hour creatinine excretion rate voids the test. Nevertheless, in cases where estimates of creatinine clearance from serum creatinine are unreliable, creatinine clearance remains a useful test. These cases include "estimation of GFR in individuals with variation in dietary intake (vegetarian diet, creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting), since these factors are not specifically taken into account in prediction equations."

Estimated Values of GFR: A number of formulae have been devised to estimate ***GFR*** or $\boldsymbol{C_{cr}}$ values on the basis of serum creatinine levels. A commonly used surrogate marker to estimate of creatinine clearance is the **Cockcroft-Gault (CG) formula**,

which in turn estimates GFR in mL/min: It employs serum creatinine measurements and a patient's weight to predict the creatinine clearance. The CG formula is defined in Eq. (16):

$$eC_{Cr} = ((140 - \text{age})\ x\ \text{mass in Kg} \times (0.85 \text{ if female}))/ (72 \times \text{serum creatinine in mg/dL}) \quad (16)$$

In Eq. (16): The weight is measured in kilograms and creatinine value is measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant of 0.85 for a female patient. This formula is useful because its simplicity. For a serum creatinine in μmol/L, the Eq. (16) reduces to (17). The Constant in Eq. (17) is 1.23 for men and 1.04 for women.

$$eC_{Cr} = ((140 - \text{age})\ x\ \text{mass in Kg} \times (\text{constant}))/(\text{Serum creatinine in } \mu\text{mol/L}) \quad (17)$$

The Cockcroft and Gault Eq. (16) is dependent on the age of a person. This means that a 20-year-old person (140–20 = 120) will have twice the creatinine clearance as an 80-year-old (140–80 = 60) for the same level of serum creatinine. The CG equation assumes that a woman will have a 15% lower creatinine clearance than a man at the same level of serum creatinine.

Estimated GFR (eGFR) Using Modification of Diet in Renal Disease (MDRD Formula)*:* The most recently advocated formula for calculating the GFR is the one that was developed by the MDRD Study Group. Most laboratories in Australia, and the United Kingdom now calculate and report the MDRD estimated GFR along with creatinine measurements and this forms the basis of Chronic kidney disease Staging. The adoption of the automatic reporting of MDRD-eGFR has been widely criticized. The most commonly used formula is the "4-variable MDRD," which estimates GFR using four variables: serum creatinine, age, race, and gender. The original MDRD used six variables with the additional variables being the blood urea nitrogen and albumin levels. The equations have been validated in patients with chronic kidney disease; however both versions underestimate the GFR in healthy patients with GFRs over 60 mL/min. The Eqs. (18) and (19) have not been validated in acute renal failure. Creatinine levels in μmol/L can be converted to mg/dL by dividing them by 88.4. The constant 32788 in Eq. (18)= 186 × 88.41.

For creatinine in μmol/L:

$$\text{eGFR} = 32788 \times (\text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}) \times (1.212 \text{ if black}) \times (0.742 \text{ if female}) \quad (18)$$

For creatinine in mg/dl:

$$\text{eGFR} = 186 \times (\text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}) \times (1.212 \text{ if black}) \times (0.742 \text{ if female}) \quad (19)$$

A more elaborate version of the MDRD equation also includes serum albumin and blood urea nitrogen (BUN) levels:

$$\text{eGFR} = 170 \times (\text{serum creatinine}^{-0.999} \times \text{age}^{-0.176}) \times (1.18 \text{ if black}) \times (0.762 \text{ if female}) \times \text{BUN}^{-0.170} \times \text{Albumin}^{+0.318} \quad (20)$$

In equation/20, the creatinine and blood urea nitrogen concentrations are measured in mg/dL. The albumin concentration is in g/dL. These MDRD equations are only used if the laboratory has not calibrated its serum creatinine measurements to isotope dilution mass spectrometry (IDMS). When IDMS-calibrated serum creatinine is used (which is about 6% lower), the above equations should be multiplied by 0.94086 = (175/186). Since these formulae do not adjust for body mass, these (relative to the Cockcroft-Gault formula) underestimate eGFR for heavy people and overestimate it for underweight people.

Estimated GFR (eGFR) Using the CKD-EPI Formula: The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was published in May 2009. It was developed in an effort to create a more accurate formula than the MDRD formula, especially when actual GFR is greater than 60 mL/min per 1.73 m^2. Researchers pooled data from multiple studies to develop and validate this new equation. They used 10 studies that included 8254 participants, randomly using 2/3 of the datasets for development and the other 1/3 for internal validation. Sixteen additional studies, which included 3896 participants, were used for external validation. The CKD-EPI equation performed better than the MDRD equation, especially at higher GFR, with less bias and greater accuracy. When looking at NHANES (National Health and Nutrition Examination Survey) data, the median estimated GFR was 94.5 mL/min per 1.73 m^2 versus 85.0 mL/min per 1.73 m^2, and the prevalence of chronic kidney disease was 11.5% versus 13.1%. In the CKD-EPI Eq. (20): SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is a constant = −0.329 for females and = −0.411 for males, min indicates the minimum of (SCr/k) or 1, and max indicates the maximum of (SCr/k) or 1. The formula CKD-EPI may provide improved cardiovascular risk prediction over the MDRD Study formula in a middle-age population.

$$\text{eGFR} = 141 \times \min(\text{SCr/k},1)^{a} x \max(\text{SCr/k},1)^{-1.2°9} \times (0.993)^{\text{age}} x\ (1.159 \text{ if black}) \times (1.018 \text{ if female}) \quad (20)$$

For Creatinine (IDMS Calibrated) in mg/dL, Levey et al. simplified the Eq. (20) for following cases:

Black female and serum creatinine (Scr) <= 0.7

$$\text{eGFR} = 166 \times (\text{SCr}/0.7)^{-0.32}9 \times (0.993)^{\text{age}} \quad (21)$$

Black female and serum creatinine (Scr) > 0.7

$$\text{eGFR} = 166 \times (\text{SCr}/0.7)^{-1.20}9 \times (0.993)^{\text{age}} \quad (22)$$

Black male and serum creatinine (Scr) <= 0.9

$$\text{eGFR} = 163 \times (\text{SCr}/0.0.9)^{-0.41}1 \times (0.993)^{\text{age}} \quad (23)$$

Black male and serum creatinine (Scr) > 0.9

$$\text{eGFR} = 163 \times (\text{SCr}/0.9)^{-1.2°9} \times (0.993)^{\text{age}} \quad (24)$$

White or other race female and serum creatinine (Scr) <= 0.7

$$\text{eGFR} = 144 \times (\text{SCr}/0.7)^{-0.32}9 \times (0.993)^{\text{age}} \quad (25)$$

White or other race female and serum creatinine (Scr) > 0.7

$$eGFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{age} \quad (26)$$

White or other race male and serum creatinine (Scr) <= 0.9

$$eGFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{age} \quad (27)$$

White or other race male and serum creatinine (Scr) > 0.9

$$eGFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{age} \quad (28)$$

Estimated GFR (eGFR) Using the Mayo Quadratic Formula: This formula was developed by Rule et al. in an attempt to better estimate GFR in patients with preserved kidney function. It is well recognized that the MDRD formula tends to underestimate GFR in patients with preserved kidney function. In Eq. (29): If serum creatinine < 0.8 mg/dL, use 0.8 mg/dL for serum creatinine.

$$eGFR = \exp\{1.911 + (5.249/\text{Seum creatinine}) - (2.114/(\text{serum creatinine})^2) - 0.00686 \times \text{age} - (0.205 \text{ if female})\} \quad (29)$$

Estimated GFR for Children Using Schwartz Formula: In children, the Schwartz developed Eq. (30). This employs the serum creatinine (mg/dL), the child's height (cm) and a constant (***k***) to estimate the glomerular filtration rate that depends on muscle mass, which itself varies with a child's age: In first year of life, for preterm babies K= 0.33, for full-term infants K= 0.45, and for infants/children of age 1 to 12 years, K= 0.55.

$$eGFR = (k \times \text{height})/(\text{serum creatnine}) \quad (30)$$

The method of selection of the K-constant value has been questioned as being dependent upon the gold-standard of renal function used (i.e., creatinine clearance, inulin clearance, etc.) and also may be dependent upon the urinary flow rate at the time of measurement. In 2009, the Eq. (30) was updated to use standardized serum creatinine (recommend k = 0.413) and additional formulas that allow improved precision were derived if serum cystatin measured in addition to serum creatinine.

Importance of Calibration of the Serum Creatinine Level and the IDMS Standardization Effort: One problem with any creatinine-based equation for GFR is that the methods used to assay creatinine in the blood differ widely in their susceptibility to nonspecific chromogens, which cause the creatinine value to be overestimated. In particular, the MDRD equation was derived using serum creatinine measurements that had this problem. The NKDEP program in the United States has attempted to solve this problem by trying to get all laboratories to calibrate their measures of creatinine to a "gold standard" which in this case is isotope dilution mass spectrometry (IDMS). In late 2009 not all laboratories in the U.S. had changed over to the new system. There are two forms of the MDRD equation that are available, depending on whether or not creatinine was measured by an IDMS-calibrated assay. The CKD-EPI equation is designed for IDMS-calibrated serum creatinine values only.

8.2.6.3 ESTIMATION OF GFR USING CYSTATIN-C

Problems with creatinine (varying muscle mass, recent meat ingestion, etc.) have led to evaluation of alternative methods for estimation of GFR. One of these is cystatin C: a ubiquitous protein secreted by most cells in the body (it is an inhibitor of cysteine protease). Cystatin-C is freely filtered at the glomerulus. After filtration, Cystatin-C is reabsorbed and catabolized by the tubular epithelial cells, with only small amounts excreted in the urine. Cystatin-C levels are therefore measured not in the urine, but in the bloodstream.

Cystatin C or cystatin 3 (formerly gamma trace, postgamma-globulin or neuroendocrine basic polypeptide), a protein encoded by the CST3 gene, is mainly used as a biomarker of kidney function. Recently, it has been studied for its role in predicting new-onset or deteriorating cardiovascular disease. It also seems to play a role in brain disorders involving amyloid (a specific type of protein deposition), such as Alzheimer's disease. In humans, all cells with a nucleus (cell core containing the DNA) produce cystatin C as a chain of 120 amino acids. It is found in virtually all tissues and body fluids. It is a potent inhibitor of lysosomal proteinases (enzymes from a special subunit of the cell that break down proteins) and probably one of the most important extracellular inhibitors of cysteine proteases (it prevents the breakdown of proteins outside the cell by a specific type of protein degrading enzymes). Cystatin C belongs to the type 2 cystatin gene family. Cystatin C was first described as 'gamma-trace' in 1961 as a trace protein together with other ones (such as beta-trace) in the cerebrospinal fluid and in the urine of patients with renal failure. Grubb and Löfberg first reported its amino acid sequence. They noticed it was increased in patients with advanced renal failure. It was first proposed as a measure of glomerular filtration rate by Grubb and et al. (1985). Cystatin C levels have been reported to be altered in patients with cancer, (even subtle) thyroid dysfunction and glucocorticoid therapy in some but not all situations. Other reports have found that levels are influenced by cigarette smoking and levels of C-reactive protein.

The GFR, a marker of kidney health, is best measured by injecting compounds such as inulin, radioisotopes such as ^{51}chromium-EDTA, ^{125}I-iothalamate, ^{99}mTc-DTPA or radiocontrast agents such as iohexol, but these techniques are complicated, costly, and time-consuming and have potential side-effects. *Creatinine is the most widely used biomarker of kidney function.* It is inaccurate at detecting mild renal impairment, and levels can vary with muscle mass and protein intake. Formulas such as the Cockcroft and Gault formula and the MDRD formula try to adjust for these variables. Cystatin C has a low molecular weight (approximately 13.3 kilodaltons), and it is removed from the bloodstream by glomerular filtration in the kidneys. If kidney function and glomerular filtration rate decline, the blood levels of cystatin C rise. Serum levels of cystatin C are a more precise test of kidney function (as represented by the glomerular filtration rate, GFR) than serum creatinine levels. This finding is based mainly on cross-sectional studies (on a single point in time). Longitudinal studies (that follow cystatin C over time) are limited; some studies show promizing results. Cystatin C levels are less dependent on age, sex, race and muscle mass compared to creatinine. Cystatin C measurements alone have not been shown to be superior to formula-adjusted estimations of kidney function. As opposed to previous claims, cystatin C has been found to

be influenced by body composition. It has been suggested that cystatin C might predict the risk of developing chronic kidney disease, thereby signaling a state of 'preclinical' kidney dysfunction. Studies have also investigated cystatin C as a marker of kidney function in the adjustment of medication dosages.

Cystatin C levels seem to be increased in HIV infection, which might or might not reflect actual renal dysfunction. The role of cystatin C to monitor GFR during pregnancy remains controversial. Like creatinine, the elimination of cystatin C via routes other than the kidney increase with worsening GFR. Cystatin C can be measured in a random sample of serum (the fluids in blood from which the red blood cells and clotting factors have been removed) using immunoassays such as nephelometry or particle-enhanced turbidimetry. It is a more expensive test than serum creatinine (around $2 or $3 compared to $0.02 to $0.15), which can be measured with a Jaffé reaction.

Reference values of cystatin C (in mg/L) differ in many populations and with sex and age. Across different studies, the mean reference interval (as defined by the 5th and 95th percentile) was between 0.52 and 0.98 mg/L. For women, the average reference interval is 0.52 to 0.90 mg/L with a mean of 0.71 mg/L. For men, the average reference interval is 0.56 to 0.98 mg/L with a mean of 0.77 mg/L. The normal values decrease until the first year of life, remaining relatively stable before they increase again, especially beyond age 50. Creatinine levels increase until puberty and differ according to gender from then on, making their interpretation problematic for pediatric patients. In a large study from the United States National Health and Nutrition Examination Survey, the reference interval (as defined by the 1st and 99th percentile) was between 0.57 and 1.12 mg/L. This interval was 0.55–1.18 for women and 0.60–1.11 for men. Non-Hispanic blacks and Mexican Americans had lower normal cystatin C levels. Other studies have found that in patients with an impaired renal function, women have lower and blacks have higher cystatin C levels for the same GFR. For example, the cut-off values of cystatin C for chronic kidney disease for a 60-year-old white women would be 1.12 mg/L and 1.27 mg/L in a black man (a 13% increase). For serum creatinine values adjusted with the MDRD equation, these values would be 0.95 mg/dL to 1.46 mg/dL (a 54% increase). Based on a threshold level of 1.09 mg/L (the 99th percentile in a population of 20 to 39-year-olds without hypertension, diabetes, microalbuminuria or macroalbuminuria or higher than stage 3 chronic kidney disease), the prevalence of increased levels of cystatin C in the United States was 9.6% in subjects of normal weight, increasing in overweight and obese individuals. In Americans aged 60 and 80 and older, serum cystatin is increased in 41% and more than 50%.

Equations have been developed linking estimated GFR to serum cystatin-C levels. Most recently, some proposed equations have combined (sex, age and race) adjusted cystatin-C and creatinine. The most accurate is (sex, age and race) adjusted cystatin-C, followed by (sex, age and race) adjusted creatinine and then cystatine-C alone in slightly different with adjusted creatinine. Inker et al. reported in the July 5, 2012 issue of the New England Journal of Medicine (367(1):20–29): "Estimates of glomerular filtration rate (GFR) that are based on serum creatinine are routinely used; however, they are imprecise, potentially leading to the overdiagnosis of chronic kidney disease. Cystatin C is an alternative filtration marker for estimating GFR. The combined creatinine-cystatin C equation performed better than equations based on either of these

markers alone and may be useful as a confirmatory test for chronic kidney disease." At Department of Clinical Chemistry, University of Lund – Sweden, Dr. Anders O. Grubb has conducted in depth studies on cystatin-C versus human health. In his article titled, Cystatin C – properties and use as diagnostic markerin Advances in Clinical Chemistry 2000(35):63–69, he concluded: "The good correlation allows close estimation of GFR. Reference Range for Cystatin C was ≤ 0.95 mg/l in men and women, and children > 1 year showed adult levels. Higher levels of Cystatin C in elderly healthy subjects > 60 years reflected increased sensitivity for the age-related GFR decline. Levels were not influenced by muscle mass or any analytical interfering factors. Inulin clearance and serum Cystatin C testing in 209 patients with a broad range of GFR, age and different pathologies yielded the correlation equation below for calculation of estimated GFR."

$$eGFR = (74.835)/(CystatinC^{(1/0.75)}) \quad (31)$$

Ratios for the evaluation of the kidney performance are listed below:

Renal plasma flow, RPF RPF = Effectice RPF/Extraction ratio (32)	Volume of blood plasma delivered to the kidney per unit time. PAH clearance is a renal analysis method used to provide an estimate. Approximately 625 mL/min.
Renal blood flow, RBF RBF = (RPF)/(1 – HCT)(33)	Volume of blood delivered to the kidney per unit time. In humans, the kidneys together receive roughly 20% of cardiac output, amounting to one L/min in a 70-kg adult male. Here: HCT is hematocrit.
Glomerular filtration rate, GFR: Estimated using creatinine clearance $eGFR = (U_{creatinine}\ x\ (dV/dt))/P_{creatinine}$ (34)	Volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time. Estimated using inulin. Usually a creatinine clearance test is performed but other markers, such as the plant polysaccharide inulin or radiolabeled EDTA, may be used as well. Measures portion of renal plasma that is filtered.
Filtration fraction, FE FE = (GFR/RPF) (35)	The filtration fraction is the amount of plasma which is actually filtered through the kidney. Normal value of human ***FE*** is 20%. RPF is a renal plasma flow.
Anion gap, AG $AG = (Na+) – \{(Cl–) + (HCO_{3–})\}$ (36)	Cations minus anions. Excludes K^+ (usually), Ca^{2+}, $H_2PO_{4–}$ Aids in the differential diagnosis of metabolic acidosis.

Clearance (other than water), C $C = (U\ x\ (dV/dt))/P$ (37)	Rate of removal. Here: U = concentration, V = urine volume/time, U*(dV/dt) = urinary excretion, and P = plasma concentration.
Free water clearance, $C_{H2}O$ $C = (dV/dt) - CO_{sm}$ or $(dV/dt)\ (1 - (UO_{sm}/PO_{sm}) = C_{H2}O$(38)	The volume of blood plasma that is cleared of solute-free water per unit time.
Net acid excretion, NEA $NEA = (dV/dt)\ (U_{NH4} + U_{TA} - U_{H}CO_{3})$ (39)	Net amount of acid excreted in the urine per unit time.

Urinary system physiology (Renal physiology and acid-base physiology) includes in depth study of topics listed below. A detailed description of each topic is beyond the scope of this book.

1. **Filtration:** Renal blood flow, ultrafiltration, countercurrent exchange, filtration fraction.
2. **Hormones affecting filtration**: Antidiuretic hormone (ADH), aldosterone, atrial natriuretic peptide.
3. **Secretion/clearance**: Pharmacokinetics, clearance of medications, urine flow rate.
4. **Reabsorption:** Solvent drag, Na+, Cl-, urea, glucose, oligopeptides, and protein.
5. **Endocrine:** Renin, erythropoietin (EPO), calcitriol (active vitamin D), and prostaglandins.
6. **Assessing renal function/measures of dialysis**: Glomerular filtration rate, creatinine clearance, renal clearance ratio, urea reduction ratio, Kt/V, standardized Kt/V, hemodialysis product, PAH clearance (Effective renal plasma flow extraction ratio).
7. **Acid-base physiology:** Fluid balance, Darrow Yannet diagram, body water (Intracellular fluid/Cytosol, Extracellular fluid (Interstitial fluid, Plasma and Transcellular fluid), base excess, Davenport diagram.
8. **Anion gap:** Arterial blood gas, Winter's formula.
9. **Buffering/compensation:** Bicarbonate buffering system, respiratory compensation, renal compensation.
10. **Other:** Fractional sodium excretion, BUN-to-creatinine ratio, tubuloglomerular feedback, natriuresis, urine.

We can summarize that the kidney participates in whole-body homeostasis, regulating acid-base balance, electrolyte concentrations, extracellular fluid volume, and regulation of blood pressure. The kidney accomplishes these homeostatic functions both independently and in concert with other organs, particularly those of the endocrine system. Various endocrine hormones coordinate these endocrine functions; these include renin, angiotensin II, aldosterone, antidiuretic hormone, and atrial natriuretic peptide, among others. Many of the kidney's functions are accomplished by relatively simple mechanisms of filtration, reabsorption, and secretion, The kidney generates

180 liters of filtrate a day, while reabsorbing a large percentage, allowing for the generation of only approximately two liters of urine. Reabsorption is the transport of molecules from this ultrafiltrate and into the blood. Secretion is the reverse process, in which molecules are transported in the opposite direction, from the blood into the urine. The kidneys excrete a variety of waste products produced by metabolism. These include the nitrogenous wastes called "urea," from protein catabolism, as well as uric acid, from nucleic acid metabolism. Formation of urine is also the function of the kidney. The concentration of nitrogenous wastes, in the urine of mammals and some birds, is dependent on an elaborate countercurrent multiplication system. This requires several independent nephron characteristics to operate: a tight hair pin configuration of the tubules, water and ion permeability in the descending limb of the loop, water impermeability in the ascending loop and active ion transport out of most of the ascending loop. In addition, countercurrent exchange by the vessels carrying the blood supply to the nephron is essential for enabling this function. Glucose at normal plasma levels is completely reabsorbed in the proximal tubule. The mechanism for this is the Na+/glucose cotransporter. A plasma level of 350 mg/dL will fully saturate the transporters and glucose will be lost in the urine. A plasma glucose level of approximately 160 is sufficient to allow glucosuria which is an important clinical clue to diabetes mellitus. Amino acids are reabsorbed by sodium dependent transporters in the proximal tubule. Hartnup's disease is a deficiency of the tryptophan amino acid transporter which results in pellagra. Pregnancy reduces the reabsorption of glucose and amino acids. Location of reabsorption of nutrients is summarized below:

Location of Reabsorption	**Reabsorbed nutrient**	**Observations**
Early proximal tubule	Glucose (100%), amino acids (100%), bicarbonate (90%), Na+ (65%), Cl-, phosphate and H_2O (65%)	PTH will inhibit phosphate excretion AT II stimulates Na+, H_2O and HCO3- reabsorption.
Thin descending loop of Henle	H_2O	Reabsorbs via medullary hypertonicity and makes urine hypertonic.
Thick ascending loop of Henle	Na+ (10–20%), K+, Cl-; Indirectly induces paracellular reabsorption of Mg2+, Ca2+	This region is impermeable to H_2O and the urine becomes less concentrated as it ascends.
Early distal convoluted tubule	Na+ and Cl-	PTH causes Ca^{2+} reabsorption.
Collecting tubules	Na+(3–5%), H_2O	Na^+ is reabsorbed in exchange for K^+ and H^+ which is regulated by aldosterone. ADH acts on the V2 receptor and inserts aquaporins on the luminal side.

8.2.6.4 ACID-BASE HOMEOSTASIS

Two organ systems, the kidneys and lungs, maintain acid-base homeostasis, which is the maintenance of pH around a relatively stable value. The lungs contribute to acid-base homeostasis by regulating carbon dioxide (CO_2) concentration. The kidneys have two very important roles in maintaining the acid-base balance: to reabsorb bicarbonate from urine, and to excrete hydrogen ions into urine

8.2.6.5 OSMOLALITY REGULATION

Any significant rise in plasma osmolality is detected by the hypothalamus, which communicates directly with the posterior pituitary gland. An increase in osmolality causes the gland to secrete antidiuretic hormone (ADH), resulting in water reabsorption by the kidney and an increase in urine concentration. The two factors work together to return the plasma osmolality to its normal levels. ADH binds to principal cells in the collecting duct that translocate aquaporins to the membrane, allowing water to leave the normally impermeable membrane and be reabsorbed into the body by the vasa recta, thus increasing the plasma volume of the body. There are two systems that create a hyperosmotic medulla and thus increase the body plasma volume: Urea recycling and the 'single effect.' Urea is usually excreted as a waste product from the kidneys. However, when plasma blood volume is low and ADH is released the aquaporins that are opened are also permeable to urea. This allows urea to leave the collecting duct into the medulla creating a hyperosmotic solution that 'attracts' water. Urea can then reenter the nephron and be excreted or recycled again depending on whether ADH is still present or not. The 'Single effect' describes the fact that the ascending thick limb of the loop of Henle is not permeable to water but is permeable to NaCl. This allows for a countercurrent exchange system whereby the medulla becomes increasingly concentrated, but at the same time setting up an osmotic gradient for water to follow should the aquaporins of the collecting duct be opened by ADH.

8.2.6.6 BLOOD PRESSURE REGULATION

Although the kidney cannot directly sense blood, long-term regulation of blood pressure predominantly depends upon the kidney. This primarily occurs through maintenance of the extracellular fluid compartment, the size of which depends on the plasma sodium concentration. Renin is the first in a series of important chemical messengers that make up the renin-angiotensin system. Changes in renin ultimately alter the output of this system, principally the hormones angiotensin II and aldosterone. Each hormone acts via multiple mechanisms, but both increase the kidney's absorption of sodium chloride, thereby expanding the extracellular fluid compartment and raizing blood pressure. When renin levels are elevated, the concentrations of angiotensin II and aldosterone increase, leading to increased sodium chloride reabsorption, expansion of the extracellular fluid compartment, and an increase in blood pressure. Conversely, when renin levels are low, angiotensin II and aldosterone levels decrease, contracting the extracellular fluid compartment, and decreasing blood pressure.

8.2.6.7 FORMATION OF URINE

The nephrons make urine by filtering the blood of its small molecules and ions and then reclaiming the needed amounts of useful materials. Surplus or waste molecules

and ions are left to flow out as urine. In 24 hr, the adult kidneys reclaim about 1300 g of NaCl, 400 g of $NaHCO_3$ and 180 g of glucose out of 180 liters of water that enters the tubules.

The process includes: Blood enters the glomerulus under pressure; this causes water, small molecules (but not macromolecules like proteins) and ions to filter through the capillary walls into the Bowman's capsule. The nephric filtrate is simply blood plasma minus almost all of the plasma proteins (Table 1). Essentially it is similar to interstitial fluid. Table 2 shows physical and chemical properties of urine.

Nephric filtrate collects within the Bowman's capsule and then flows into the proximal tubule. Here all of the glucose, and amino acids, >90% of the uric acid, and about 60% of inorganic salts are reabsorbed by active transport. The active transport of Na^+ out of the proximal tubule is controlled by angiotensin II. The active transport of phosphate (PO_4^{3-}) is regulated (suppressed) by the parathyroid hormone. As these solutes are removed from the nephric filtrate, a large volume of the water follows these solutes by osmosis (80–85% of deposited in the Bowman's capsules in 24 h). As the fluid flows into the descending segment of the loop of Henle, water continues to leave by osmosis because the interstitial fluid is very hypertonic. This is caused by the active transport of Na^+ out of the tubular fluid as it moves up the ascending segment of the loop of Henle. In the distal tubules, more sodium is reclaimed by active transport, and still more water follows by osmosis. Final adjustment of the sodium and water content of the body occurs in the collecting tubules.

8.2.6.8 SODIUM

Although 97% of the sodium is almost removed, yet the remaining 3% determines the final balance of sodium – and therefore water content and blood pressure – in our body. The reabsorption of sodium in the distal tubule and the collecting tubules is closely regulated, chiefly by the action of the hormone aldosterone.

8.2.6.9 WATER

The hypertonic interstitial fluid surrounding the tubules provides a high osmotic pressure for the removal of water. Transmembrane channels made of a protein called aquaporin are inserted in the plasma membrane greatly increasing its permeability to water. When open, an aquaporin channel allows 3 billion molecules of water to pass through each second.

Insertion of these water channels requires signaling by the antidiuretic hormone (ADH: also known as arginine vasopressin). ADH binds to receptors (called V2 receptors) on the surface of the cells of the collecting tubules.

TABLE 1 Chemical composition of plasma, nephric filtrate, and urine (28).

Component	Plasma	Nephric Filtrate	Urine	Concen-tration	% Reclaimed
All values are in g/100 mL of fluid					
Urea	0.03	0.03	1.8	60X	50
Uric acid	0.004	0.004	0.05	12X	91

TABLE 1 *(Continued)*

Component	Plasma	Nephric Filtrate	Urine	Concen-tration	% Reclaimed
Glucose	0.1	0.1	None	—	100
Amino acids	0.05	0.05	None	—	100
Total inorganic salts	0.9	0.9	< 0 . 9 – 3.6	<1–4X	99.50
Proteins and other macromolecules	8	None	None	—	—

TABLE 2 Typical laboratory urine analysis.

Properties	Units	Range
Color	—	Yellow
Turbidity	—	Clear
Specific Gravity	—	1.005–1.030
Reaction pH	—	4.6–8.0
Occult blood	—	Negative
Glucose	—	Negative
Bilirubin	—	Negative
Ketone	—	Negative
Protein	—	Negative
Urobilinogen	—	0.3–1.0
Nitrite	—	Negative
Leukocytes	—	Negative
RBC	/HPF	0–2
WBC	/HPF	0–5
Bacteria	/HPF	None to Few
Mucous	/LPF	None
Crystals	/LPF	None
Amorphous Urates	/HPF	None
Yeast Cells	—	None
Trichomonas	/HPF	None
CAST	/LPF	None
Epithelial Cells	—	Negative
Squamous	/HPF	None to Few
Transitional	/HPF	None to Few
Renal	/HPF	None
Oval fat Bodies	/HPF	None

Binding of the hormone triggers a rising level of cAMP (3′,5′-cyclic adenosine monophosphate) within the cell. This "second messenger" initiates a chain of events culminating in the insertion of aquaporin channels. The release of ADH (from the posterior lobe of the pituitary gland) is regulated by the osmotic pressure of the blood.

Anything that dehydrates the body increases the osmotic pressure of the blood and turns on the ADH ≥ V2 receptors ≥ aquaporin pathway. This result in: As little as 0.5 liter/day of urine may remain of the original 180 liters/day of nephric filtrate. The concentration of salts in the urine can be as high as four times that of the blood. If the blood becomes too dilute then ADH secretion is inhibited. A large volume of watery urine is formed (with a salt concentration as little as one-fourth of that of the blood).

8.3 KIDNEY DISEASES AND DISORDERS

Nephrology is the medical specialty concerned with kidney diseases. Most kidney diseases attack the nephrons, causing them to lose the filtering capacity. Damage to the nephrons may happen quickly, often as a result of injury or poisoning. But most kidney diseases destroy the nephrons slowly and silently, and attack both kidneys simultaneously. The two most common causes of kidney disease are diabetes and high blood pressure.

8.3.1 INHERITED AND CONGENITAL KIDNEY DISEASES

Some kidney diseases result from hereditary factors. Polycystic kidney disease (PKD) is a genetic disorder in which many cysts grow in the kidneys. PKD cysts can slowly replace much of the mass of the kidneys thus reducing kidney function and leading to kidney failure. The most common form of PKD was once called "adult PKD" because the symptoms of high blood pressure and renal failure usually do not occur until patients are in their twenties or thirties. But with advances in diagnostic imaging technology, doctors can find cysts in children and adolescents before any symptoms appear. Some kidney problems may show up when a child is still developing in the womb. Examples include autosomal recessive PKD and other developmental problems that interfere with the normal formation of the nephrons. The signs of kidney disease in children vary. A child may grow unusually slowly: may vomit often, or may have back or side pain. Some hereditary kidney diseases may not be detected until adulthood.

8.3.2 OTHER CAUSES OF KIDNEY DISEASE

The origin of other possible causes for kidney disease may be infectious, traumatic, vascular, metabolic, immunologic or degenerative. Some overthe-counter medicines can be poisonous to the kidneys if taken regularly over a long period of time. Products that combine aspirin, acetaminophen, and other medicines such as ibuprofen can be the dangerous to the kidneys.

8.3.3 HYPERTENSION

Hypertension is a condition in which blood pressure is persistently elevated (it stays high for a long period of time). Blood pressure is a measure of the pressure of the blood against the blood vessel walls. Therefore, high blood pressure damages the

small blood vessels in the kidneys. The damaged vessels cannot filter wastes from the blood as they are supposed to.

High blood pressure is a serious health risk. Persistent high blood pressure puts undue stress on the heart, blood vessels and other organs. Hypertension can cause heart and kidney diseases, heart attacks and strokes, as well as hardening of the arteries. Specifically case of the kidneys, high blood pressure can narrow and thicken their blood vessels. As a consequence, the kidneys filter less fluid, and waste builds up in the blood, all these resulting in the kidneys failure. When this happens, the medical treatment called dialysis or a kidney transplant may be needed. Hypertension treatment reduces the symptoms of high blood pressure and includes blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been found to protect the kidneys even more than other medicines that lower blood pressure to similar levels. The National Heart, Lung, and Blood Institute (NHLBI) recommends that people with diabetes or reduced kidney function should keep the blood pressure below 130/80 mm Hg.

Causes of high blood pressure are almost unknown. About 5% of patients requiring hypertension treatment can trace the high blood pressure to the physical cause of kidney disease. For the other 95% of patients who undergo hypertension treatment, the causes of high blood pressure are unknown. Diet and stress are suspected as prime contributors to hypertension, but medical experts aren't exactly certain of all the mechanisms involved.

8.3.4 GLOMERULONEPHRITIS (GN)

It is a renal disease (usually of both kidneys) characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. It may present with isolated hematuria and/or proteinuria (blood or protein in the urine); or as a nephrotic syndrome, a nephritic syndrome, acute renal failure, or chronic renal failure. They are categorized into several different pathological patterns, which are broadly grouped into nonproliferative or proliferative types. Diagnosing the pattern of GN is important because the outcome and treatment differs in different types. Primary causes are intrinsic to the kidney. Secondary causes are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (Systemic lupus erythematosus or SLR, vasculitis), or diabetes.

Several different types of kidney disease are grouped together under this category. Protein, blood, or both in the urine are often the first signs of these diseases. They can slowly destroy the kidney function. Blood pressure control is important, and different treatments for the different types of GN may be used.

8.3.5 END-STAGE RENAL DISEASE

The condition of total or nearly total and permanent kidney failure is called end-stage renal disease (ESRD). People with ESRD must undergo dialysis or transplantation to stay alive.

8.3.6 RENAL DYSFUNCTION

Renal dysfunction or renal failure is the suboptimal functioning of the kidneys due to kidney disease. Moreover it is a sudden or gradual loss of the kidney's ability to

excrete wastage. There are two types of renal failure: the sudden set on, occurring in days or weeks, is medically termed as acute renal failure, and the gradual, occurring in months or years, as chronic renal failure. A decrease in renal function is sufficient to result in retention in the body of nitrogenous waste such as blood, urea, nitrogen and creatinine. The hallmark of renal failure is progressive azotaemia caused by the accumulation of the nitrogenous end products of metabolism. This accumulation is accompanied by a wide-range of other disturbances depending on the severity and duration of the renal dysfunction. These include metabolic derangements such as metabolic acidosis and hyperkalemia, disturbances of body fluid balance and effects on many other organ systems.

8.3.6.1 ACUTE RENAL FAILURE (ARF)

Some kidney problems happen quickly, like an accident that injures the kidneys. Losing a lot of blood can cause sudden kidney failure. Some drugs or poisons can make the kidneys stop working. These sudden drops in kidney function are called acute renal failure. ARF may lead to permanent loss of kidney function. But if the kidneys are not seriously damaged, acute renal failure may be reversed. ARF is associated with ischemia, the reduction in blood flow, acute glomerulonephritis (glomerular nephritis, GN), tubular necrosis or poisoning with nephrotoxins.

8.3.6.2 CHRONIC KIDNEY DISEASE (CKD)

Most kidney problems, however, happen slowly. A person may have "silent" kidney disease for years. Gradual loss of kidney function is called chronic kidney disease or chronic renal insufficiency. CKD is caused by chronic gromerulonephritis, hypertension, vascular disease or pyelonephritis, which is an infection of the urinary track. Persons with CKD may experience permanent kidney failure. They also have a high risk of dying from a stroke or heart attack.

8.3.6.3 CAUSES FOR RENAL FAILURE

There are three major causes for renal failure: those that decrease renal blood flow, known as prerenal, those that produce a renal parenchymal insult, known as intrarenal, and those that obstruct urine flow, known as postrenal.

Prerenal results from a decrease in renal blood flow. The glomerular filtration rate is reduced and the kidney retains water and salt, causing oliguria, production of concentrated urine and a progressive inability to excrete nitrogenous wastes. The decrease in renal blood flow causes damage to the kidney. Also acute renal failure may occur when there is extremely low blood pressure, and consequently the patient may suffer from trauma, septic shock, hemorrhage, severe vomiting, diarrhea, burns and associated dehydration or other severe or complicated illness.

Intra renal refers to the renal failure that occurs when the internal structures of the kidney are suddenly or slowly destroyed. It is a complex collection of disease processes with a poorly understood pathophysiology. An inflammatory process is initiated in the renal parenchyma in response to a wide variety of stimuli such as toxic, metabolic, infectious, immune, and infiltrative and drugs are probably the most common causes. Most acute renal failure occurs as secondary to bacterial infection particularly with streptococcal such as the impetigo and throat infections. Chronic failure commonly

noticed with hypertension and diabetes damage the vascular walls. Smoking causes atherosclerotic changes of the arterial walls. Nephrotoxic drugs and metals could ruin the cellular complex as in prolonged chemical medication. Disorders in metabolism and immunity may occur.

Post renal ocuurs due to a simple mechanical or functional obstruction to the free flow of urine precludes its excretion and renal failure. It commonly happens with kidney stones, urethral stricture and prostate enlargement.

8.3.6.4 DIAGNOSIS

Generally, humans can live normally with just one kidney, as one has more functioning renal tissue than is needed to survive. Only when the amount of functioning kidney tissue is greatly diminished does one develop chronic kidney disease. Renal replacement therapy, in the form of dialysis or kidney transplantation, is indicated when the glomerular filtration rate has fallen very low or if the renal dysfunction leads to severe symptoms.

Clinical: Many renal diseases are diagnosed on the basis of classical clinical findings. A nephrologist begins by taking a detailed clinical history and performs a physical examination. In addition to medical history and presenting symptoms, a physician will ask about medication history, family history recent infections, toxic/chemical exposures and other historical factors which may indicate an etiology for the patient's renal disease. Often, some diseases are suggested by clinical history and time course alone. For example, in a formerly healthy child with a recent upper respiratory tract infection and facial/lower limb swelling, findings of proteinuria on urinalysis, a diagnosis of minimal change disease is highly suggested. Similarly, a patient with a history of diabetes who presents with decreased urine output is most likely to be suffering from diabetic nephropathy. Often, such cases do not require extensive workup (such as with renal biopsy). A presumptive diagnosis can be made on the basis of history, physical exam and supportive laboratory studies.

Laboratory: Laboratory studies are an important adjunct to clinical evaluation for assessment of renal function. An initial workup of a patient may include a complete blood count (CBC); serum electrolytes including sodium, potassium, chloride, bicarbonate, calcium, and phosphorus; blood urea, nitrogen and creatinine; blood glucose and glycocylated hemoglobin. Glomerular filtration rate (GFR) can be calculated. Urine studies may include urine electrolytes, creatinine, protein, fractional excretion of sodium (FENA) and other studies to assist in evaluation of the etiology of a patient's renal disease. Urinalysis is used to evaluate urine for its pH, protein, glucose, specific gravity and the presence of blood/hemoglobin. Microscopic analysis can be helpful in the identification of casts, red blood cells, white blood cells and crystals.

Imaging studies: Imaging studies are important in the evaluation of structural renal disease caused by urinary tract obstruction, renal stones, renal cyst, mass lesions, renal vascular disease, and vesicoureteral reflux. Imaging techniques used most frequently include renal ultrasound and CT scan. Patients with suspected vesicoureteral reflux may undergo voiding cystourethrogram (VCUG).

Renal biopsy: The role of the renal biopsy is to diagnose renal disease in which the etiology is not clear based upon noninvasive means (clinical history, past medical

history, medication history, physical exam, laboratory studies, and imaging studies). A detailed description of renal biopsy interpretation is beyond the scope of this book. In general- a renal pathologist will perform a detailed morphological evaluation and integrate the morphologic findings with the clinical history and laboratory data, ultimately arriving at a pathological diagnosis. A renal pathologist is a physician who has undergone general training in anatomic pathology and additional specially training in the interpretation of renal biopsy specimens. Ideally, multiple core sections are obtained and evaluated for adequacy (presence of glomeruli) intraoperatively. A pathologist/pathology assistant divides the specimen(s) for submission for light microscopy, immunofluorescence microscopy and electron microscopy. The pathologist will examine the specimen using light microscopy with multiple staining techniques (hematoxylin and eosin/H&E, PAS, trichrome, silver stain) on multiple level sections. Multiple immunofluorescence stains are performed to evaluate for antibody, protein and complement deposition. Finally, ultra-structural examination is performed with electron microscopy and may reveal the presence of electron-dense deposits or other characteristic abnormalities, which may suggest an etiology for the patient's renal disease.

8.3.7 FLUID REGULATION

In relation to the kidneys, the brain monitors bloodstream levels of water, waste products, electrolytes, and red blood cells. The circulatory system has receptors to monitor blood volume also. If the water level is too low, as occurs with dehydration, the brain secretes more of ADH (antidiuretic hormone) into the bloodstream. As a result, the kidneys excrete less water into the urinary tract, retaining more fluid in the bloodstream to counteract the dehydration. The brain also increases thirst simultaneously. The final result is less urination. The urine color is more yellow than usual due to a greater concentration of waste products being excreted in relation to the amount of water being excreted. The patient will urinate less and notice a yellow color.

As we drink water to quench our thirst and rehydrate, the body takes into account this change and the brain secretes less ADH. The ability to concentrate the urine and dilute the urine is an important function of the kidneys. It is a fine tuned mechanism that is closely regulated to maintain optimum amounts of fluid in the bloodstream and organs.

Through a complicated set of biochemical pathways this ultimately leads to an increase in salt (sodium) in the bloodstream. Sodium pulls water towards it, so more sodium means more fluid in the bloodstream. The kidneys also secrete a hormone called renin.

8.3.7.1 RENIN (PLASMA RENIN ACTIVITY, PRA)

Renin, also known as an angiotensinogenase, is an enzyme that participates in the body's renin-angiotensin system (RAS)—also known as the renin-angiotensin-aldosterone axis—that mediates extracellular volume (i.e., that of the blood plasma, lymph and interstitial fluid), and arterial vasoconstriction. Thus, it regulates the body's mean arterial blood pressure.

Renin activates the renin-angiotensin system by cleaving angiotensinogen, produced by the liver, to yield angiotensin I, which is further converted into angiotensin

II by ACE, the angiotensin-converting enzyme primarily within the capillaries of the lungs. Angiotensin II then constricts blood vessels, increases the secretion of ADH and aldosterone, and stimulates the hypothalamus to activate the thirst reflex, each leading to an increase in blood pressure.

Renin is secreted from kidney cells, which are activated via signaling from the macula densa, which responds to the rate of fluid flow through the distal tubule, by decreases in renal perfusion pressure (through stretch receptors in the vascular wall), and by sympathetic nervous stimulation, mainly through beta-1 adrenoceptor activation. A drop in the rate of flow past the macula densa implies a drop in renal filtration pressure. Renin's primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys. Renin can bind to ATP6AP2, which results in a fourfold increase in the conversion of angiotensinogen to angiotensin I over that shown by soluble renin. In addition, renin binding results in phosphorylation of serine and tyrosine residues of ATP6AP2. The level of renin mRNA appears to be modulated by the binding of HADHB, HuR and CP1 to a regulatory region in the three prime untranslated regions (3' UTR).

The primary structure of renin precursor consists of 406 amino acids with a pre and a prosegment carrying 20 and 46 amino acids, respectively. Mature renin contains 340 amino acids and has a mass of 37 kDa. Human renin is secreted by at least 2 cellular pathways: a constitutive pathway for the secretion of prorenin and a regulated pathway for the secretion of mature renin. The enzyme renin is secreted by the kidney from specialized cells called granular cells of the juxtaglomerular apparatus in response to three stimuli: 1. A decrease in arterial blood pressure (that could be related to a decrease in blood volume) as detected by baroreceptors (pressuresensitive cells). This is the most direct causal link between blood pressure and renin secretion (the other two methods operate via longer pathways); 2. A decrease in sodium chloride levels in the ultrafiltrate of the nephron. This flow is measured by the macula densa of the juxtaglomerular apparatus; and 3. Sympathetic nervous system activity that also controls blood pressure, acting through the beta1 adrenergic receptors.

An overactive renin-angiotension system leads to vasoconstriction and retention of sodium and water. These effects lead to hypertension. Therefore, renin inhibitors can be used for the treatment of hypertension. This is measured by the plasma renin activity (PRA). In current medical practice, the renin-angiotensin-aldosterone-System's overactivity (and resultant hypertension) is more commonly reduced using either ACE inhibitors (such as ramipril and perindopril) or angiotensin II receptor blockers (ARBs, such as losartan, irbesartan or candesartan) rather than a direct oral renin inhibitor. ACE inhibitors or ARBs are also part of the standard treatment after a heart attack. The differential diagnosis of kidney cancer in a young patient with hypertension includes juxtaglomerular cell tumor (reninoma), Wilms' tumor, and renal cell carcinoma, all of which may produce renin.

Renin is usually measured as the plasma renin activity (PRA). PRA is measured especially in case of certain diseases that present with hypertension or hypotension. PRA is also raised in certain tumors. A PRA measurement may be compared to a plasma aldosterone concentration (PAC) as a PAC/PRA ratio.

Renin measurements are affected by salt intake, pregnancy, time of day, body position, and certain drugs (Birth control pill, blood pressure medications, diuretics, and vasodilators). Before taking a blood sample for the diagnosis and treatment of high blood pressure/PRA/PAC, the patient should temporarily stop taking certain drugs that can affect test results; and should eat a normal, balanced diet with moderate sodium content (about 3 gm/day) for 3 days before the test. Normal values renin range from 0.2 to 3.3 ng/ml/hour. Normal value ranges may vary slightly among different laboratories. High levels of renin may be due to: Addison's disease, cirrhosis, congestive heart failure, dehydration, hemorrhage (bleeding), high blood pressure, hypokalemia, malignant hypertension, nephrotic syndrome, renin-producing renal tumors, and renovascular hypertension. Low renin levels may be due to: ADH therapy, hyperaldosteronism, sodium-retaining steroid therapy, and high blood pressure that is sodium-sensitive.

8.3.8 REGULATION OF WASTE PRODUCTS

The brain also monitors waste products that build up in the bloodstream. These waste products are the end product of normal metabolic processes, especially the metabolism of proteins. They are called nitrogenous waste products, and are measured by a blood parameter called blood urea nitrogen (BUN). Another waste product that is closely regulated by the brain and kidneys is called creatinine, which is the final product of the muscle's metabolism.

The kidneys also excrete toxins and foreign substances that are introduced into the body. Almost every medication given, either orally or by injection, is eliminated to some degree by the kidneys.

The rate at which fluid flows into the glomerulus is important. This is called the glomerular filtration rate (GFR) and is measured in mL/minute. If during dehydration the flow is too small, waste products are not eliminated. Whereas if there is too much flow, normal blood constituents like protein are excreted.

8.4 ARTIFICIAL KIDNEYS

When renal failure occurs, the use of an artificial kidney is required to fulfill the functions. Table 3 indicates values of renal function parameters in mammals. An artificial kidney is a machine that provides a means for removing undesirable substances from the blood and adding needed components to it. An **artificial kidney** is often a synonym for hemodialysis, but may also refer to renal replacement therapies (with exclusion of renal transplantation) that are in use and/or in development. It may also include bioengineered kidneys/bioartificial kidneys that are grown from renal cell lines/renal tissue.

Hemodialysis is a method for removing waste products such as creatinine and urea, as well as free water from the blood when the kidneys are in renal failure. The mechanical device used to clean the blood of a patient is called a dialyzer, also known as an artificial kidney. Modern dialyzers typically consist of a cylindrical rigid casing enclosing hollow fibers cast or extruded from a polymer or copolymer, which is usually a proprietary formulation. The combined area of the hollow fibers is typically between 1 to 2 square meters. Intensive research has been conducted by many groups to optimize blood and dialysate flows within the dialyzer, in order to achieve efficient

transfer of wastes from blood to dialysate. The principle of dialysis is based on the ultrafiltration.

8.4.1 ULTRAFILTRATION

Ultrafiltration is a process of fluid removal that consists in the separation of particles from a suspension by a passage through a filter with very fine pores. The separation process is accomplished by convective transport, and water accumulated in the patient's body during dialysis is removed from the plasma. Ultrafiltration occurs naturally and is a laboratory procedure, also referred to as hemofiltration.

8.4.2 HEMOFILTRATION

Hemofiltration is an artificial ultrafiltration of the blood of a patient. It is an extracorporeal ultrafiltration technique. This technique does not include hemodialysis, and it is used for the treatment of fluid overload and electrolyte disturbances that affects renal, cardiac, or pulmonary functions. In Hemofiltration, blood is forced through a semi permeable membrane; and water and small molecules are filtered out of the blood. This process is slower and less physiologically disturbing than hemodialysis and is used in intensive care units on very sick patients.

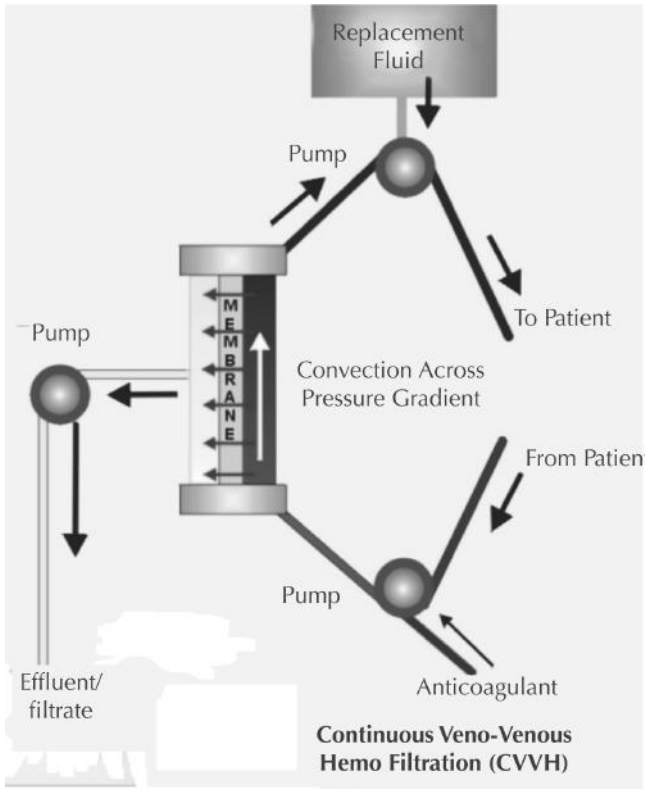

FIGURE 7 Continuous veno-venous hemofiltration (11).

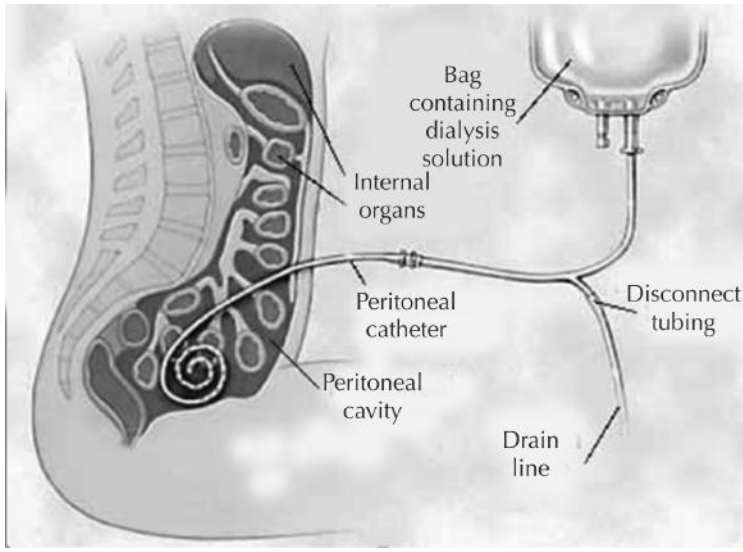

FIGURE 8 Schematic diagram of a peritoneal dialysis (24).

8.4.3 TYPES OF HEMOFILTRATION

a. **The continuous veno-venous hemofiltration** (**CVVH)** is the process that uses a pump assisted system and a prefilter or postfilter replacement solution (Fig. 7). CVVH uses convective clearance. The continuous veno-venous hemodialysis, (**CVVHD),** is the process that uses a pump assisted system and a counter current (to blood flow) solution. CVVHD uses diffusion solution clearance. **The** continuous veno-venous hemodiafiltration, **(CVVHDF),** hemofiltration uses a pump assisted system and pre or post filter replacement solution and countercurrent solution. CVVHDF uses convective and diffusive clearance. **The SCUF** is a slow continuous ultrafiltration. SCUF uses no replacement nor counter current solutions and only removes fluid.

b. **Dialysis** is a process of removing blood from a patient whose kidneys functioning is faulty, purifying that blood and returning it to the bloodstream of the patient. Like healthy kidneys, dialysis keeps our body in balance. It removes waste, salt and extra water to prevent them from building up in the body. It also keeps a safe level of certain chemicals in the blood, such as potassium, sodium and bicarbonate and helps to control blood pressure. There are two types of dialysis: peritoneal dialysis and hemodialysis. Both types result in partial correction of abnormal metabolite, fluid, electrolyte and pH levels during the treatment.

8.5 PERITONEAL DIALYSIS

In peritoneal dialysis (Fig. 8), the blood is cleaned inside the human body by means of a fluid that is put into the lining of the abdomen, which is called a peritoneal membrane. The cleansing fluid is called dialysate (Fig. 8) and travels through a small, soft tube (called a catheter) placed surgically. Fluid, wastes, and chemicals pass from tiny blood vessels in the peritoneal membrane into the dialysate. After several hours, the

dialysate gets drained from the abdomen, thus removing the wastes from the blood. Then the abdomen is filled with fresh dialysate and the cleaning process begins again. The treatments can be done at home or in a dialysis clinic. The treatment is repeated generally three times a week and may require the assistance of a nurse or family member.

TABLE 3 Renal functions in mammals (Altman 1961, pages 394–396).

Specification	Age	Value (Avg. and range)	Specification	Age	Value
Renal blood flow (ml/min/1.73 sq m body surface area)	16–60 yr	1209(697–1721)	Glomerular filtration rate (ml/min/1.73 sq m body surface area)	2–8 day	38.5(16.7–60.3)
	<20–45 yr	1076(660–1492)		4–28 day	45.1(26.1–64.1)
	20–29 yr	1077(777–1377)		10–22 day	50.4(32.2–68.6)
	30–39 yr	1181(727–1635)		37–95 mo	58.2(30.2–86.2)
	40–49 yr	1008(596–1420)		1–5.9 mo	76.6(39.4–113.8)
	50–59 yr	849(603–1095)		6–11.7 mo	103.2(49.4–157)
	60–69 yr	775(479–1053)		12–19 mo	126.7(62.1–191.3)
	70–79 yr	589(323–855)		2–12yr	127(89.4–164.6)
	80–89 yr	475(193–757)		16–49yr	124(72.4–175.6)
	16–55 yr	982(614–1350)		16–60yr	131(88–174)
	<20–45 yr	973(503–1443)		18–45yr	140(76–204)
		1359(881–1837)		20–29yr	122.8(90–155.6)
	<20–40 yr	919(451–1387)		21–25yr	125(116.2–133.8)
	Adult	962(602–1322)		28–60yr	136(97.4–174.6)
Renal plasma flow (ml/min/1.73 sq m body suface area)	2–8day	72.7		30–39yr	115(93.4–136.6)
	4–28day	148.6		40–49yr	121.2(74.6–167.8)
	10–22day	228.5		50–59yr	99.3(70.1–128.5)
	37–95day	203.2		60–69yr	96(45–147)
	1–5.9 mo	326.1		70–79yr	89(49.4–128.6)
	6–11.7 mo	480.3		80–89yr	65.3(24.5–106.1)
	12–19 mo	518.9(319.9–717.9)		adult	130(99.2–160.8)
	2–12yr	654(413–895)			126(91.8–160.2)
	16–60yr	697(425–969)		16–55yr	115(89.4–140.6)
	20–29yr	613.5(464.3–762.7)			117(85.8–148.2)

TABLE 3 *(Continued)*

Specification	Age	Value (Avg. and range)	Specification	Age	Value
	21–25yr	600(388–812)		19–27yr	118(90.2–145.8)
	30–39yr	649.3(414.5–884.1)		<20–40yr	156(95–217)
	40–49yr	573.8(350.6–797)		adult	119(111–127)
	50–59yr	500.4(326.4–674.4)			109(82–136)
	60–69yr	442.1(281.7–602.5)			183(139–227)
	70–79yr	354(187.2–520.8)			129(43–215)
	80–89yr	288.8(111.6–466)			126(68.6–183.4)
	16–55yr	594(390–798)			131(67–195)
	19–27yr	628(428–828)			126(94–158)
	<20–45yr	800(498–1102)		<20–45yr	118(79–157)
	<20–40yr	571(393–749)		20–50yr	124(97.4–150.6)
	adult	617(397–837)		<20–45yr	122(73.4–170.6)
	19–49yr	654(328–980)			170(123.6–216.4)
	21–32yr	613(399–827)		20–50yr	119(934–144.6)
	adult	628(538–718)	Filtration fraction, %	2–8day	0.49
		603(435–771)		4–28day	0.34
		592(286–898)		10–22day	0.24
	<20–45yr	557(251–863)		37–95day	0.33
		557(271–843)		1–5.9 mo	0.24
Filtration fraction, %	6–11.7 mo	0.22(0.08–0.36)	p-Aminohippurate Tm (tubular excretory mass) (mg/min/1.73 sq m body surface area)	30–39yr	87.7(61.9–113.5)
	12–19 mo	0.25(0.15–0.35)		40–49yr	79.4(60.4–98.4)
	2–12yr	0.2(0.12–0.28)		50–59yr	72.2(40.6–103.8)
	16–49yr	0.192(0.122–0.262)		60–69yr	66.2(39.6–92.8)
	16–60yr	0.19(0.142–0.238)		70–79yr	59.4(34.2–84.6)
	<20–45yr	0.216(0.152–0.28)		80–89yr	38.6(11.4–65.8)
	20–29yr	0.201(0.175–0.227)		adult	65.6(48.2–83)
	21–25yr	0.214(0.144–0.235)			77.2
	30–39yr	0.184(0.112–0.256)			77.2(55.6–98.8)

TABLE 3 *(Continued)*

Specification	Age	Value (Avg. and range)	Specification	Age	Value
	40–49yr	0.213(0.149–0.277)	Glucose Tm	4–28day	77
	50–59yr	0.205(0.142–0.265)	(tubular-absorptive	37–95day	104
	60–69yr	0.215(0.47–0.283)	mass) (mg/	2–12yr	543(285–801)
	70–79yr	0.262(0.104–0.42)	min/1.73 sq m body suface area)	20–29yr	358.7(324–395)
	80–89yr	0.229(0.153–0.305)		28–60yr	375(215–535)
	16–55yr	0.202(0.14–0.264)		30–39yr	333.6(112.6–221)
	19–27yr	0.189(0.55–0.223)		40–49yr	315.1(224.7–405.5)
	<20–45yr	0.227(0.131–0.323)		50–59yr	308.2(178.2–438.2)
		0.221(0.117–0.325)		60–69yr	260.2(131–389.4)
	<20–40	0.289(0.211–0.367)		70–79yr	239.3(146.5–332.1)
	adult	19.5		80–89yr	219.2(118.8–319.6)
		0.194(0.116–0.272)		16–55yr	303(193–413)
Diodrast Tm (tubular excretory mass) (mg I/min/1.73 sq m body suface area)	16–60yr	51.8(34.4–69.2)	Urea clearance	2–28day	17–34
	20–29yr	54.6(35.6–73.6)		54–356day	35–55
	21–25yr	50.6(37.6–63.6)	Whole blood (ml/min/1.73 sq m body suface area)	2–13yr	72–78
	30–39yr	51(33.8–68.2)		2–8day	23.2
	40–49yr	49.9(30.3–69.5)		4–28day	31.5(20.5–42.5)
	50–59yr	45.3(32.7–57.9)		10–22day	36
	60–69yr	44.5(26.3–62.7)		37–95day	40
	70–79yr	39(24.4–53.6)		1–5.9 mo	55.4(23.2–87.6)
	80–89yr	30.8(11.2–50.4)		6–11.7 mo	67.9
	adult	50		12–19 mo	71.1
	16–55yr	42.6(23.6–61.6)		2–12yr	75(38–112)
	12–27yr	44.2(34.6–53.8)		40–49yr	95(66.2–123.8)

TABLE 3 *(Continued)*

Specification	Age	Value (Avg. and range)	Specification	Age	Value
p-Aminohippurate Tm (tubular excretory mass) (mg/min/1.73 sq m body surface area)	4–28day	12.9		50–59yr	86(44.8–127.2)
	10–22day	21.4		60–69yr	82(47.2–116.8)
	37–95day	17.2		70–79yr	65(30–100)
	1–5.9 mo	51.4		80–89yr	61(11–111)
	6–11.7 mo	50.5	Plasma		79(21–137)
	12–19 mo	61.2(18.8–103.6)			77(45–109)
	2–12yr	73.7(35.9–111.5)			
	16–49yr	79.8(46.4–113.2)			
	20–29yr	108.7			

TABLE 4 Replacement fluids for dialysate (25).

Constituents	Phosphorous-based: Replacement Fluid/Dialysate	Calcium-Based: Replacement Fluid/Dialysate
NaCl (mEq/L)	60–100	60–100
NaHCO3 (mEq/L)	80–40	80–40
KCl (mEq/L)	2	2.0–4.0
K3PO4 (mEq/L)	2	0
MgSO4 (mEq/L)	0.5–1.5	0.5–1.5
Dextrose (g/L)	0–2.0 (0–0.2%)	0–0.2 (0–0.2)
CaCl2 (mEq/L)	0	3.0–4.0

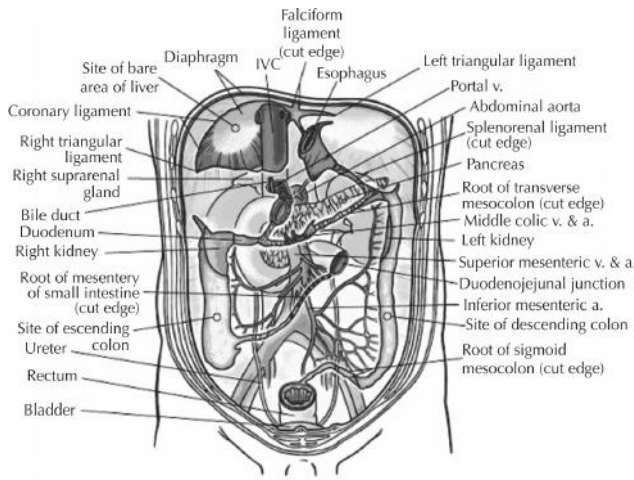

FIGURE 9 Location of the peritoneal cavity (23).

8.5.1 PHYSIOLOGICAL PRINCIPLES

The peritoneal membrane covers the abdominal cavity and has a surface area of up to two square meters. The peritoneal cavity is the potential space between the parietal membrane and the visceral membrane. The primary physiologic function of the peritoneal membrane is to line the walls of the abdominal cavity and encapsulate its internal organs. Normally this cavity contains between 50 and 100 mL of fluid, which acts as a lubricant (Fig. 9). During peritoneal dialysis, a dialysis solution is infused into the peritoneal cavity.

During peritoneal dialysis, solutes and fluids are exchanged between the capillary blood and the intraperitoneal fluid through the peritoneal membrane. The peritoneal membrane has three layers which are: (1) Mesothelium: a continuous monolayer of flat cells, and their basement membranes; (2) The interstitium; and (3) The capillary endothelium: consisting of a continuous layer of endothelial cells, supported by a basement membrane. The peritoneal membrane is semipermeable and allows the passage of both water and solutes. During peritoneal dialysis three processes are involved in removing fluid and wastes from the blood stream and balancing electrolytes. These processes are osmosis, diffusion and convection.

Osmosis is the movement of water through a semipermeable membrane from a solution of low concentration into a solution with a higher concentration. The solution into which the water moves in peritoneal dialysis contains an osmotic agent, which is usually glucose.

Diffusion is the solute exchange between two solutions, usually separated by a semipermeable membrane. The solutes travel in either direction across the membrane until the equilibrium is achieved. The direction and speed at which the solutes flow depend on the concentration gradient. Solutes will flow from the stronger solution into the weaker solution (Fig. 10). Therefore, they will pass in either direction across the peritoneal membrane. Other factors that affect diffusion rate are molecular weight and membrane resistance.

Convective flow transports water and solutes across the membrane due to the large amount of osmotic ultrafiltration that occurs during peritoneal dialysis.

8.5.2 DIALYSATE SOLUTION

The dialysate solution contains electrolytes, which are used to facilitate correction of acid-base and electrolyte abnormalities in the kidneys. High concentrations of glucose in the dialysis solution generate ultrafiltration in proportion to the osmotic gradient, the reflection coefficients of small solutes relative to the peritoneum, and the peritoneal membrane hydraulic permeability. Removal of solutes such as urea, and other metabolic end products from the body depends on the development of concentration gradients between blood and intraperitoneal fluid, and the transport is driven by the process of diffusion. Table 4 indicates replacement fluids for dialysate.

8.5.3 COEFFICIENT OF MASS TRANSFER AREA (MTAC)

MTAC is the clearance rate by diffusion in the absence of ultrafiltration and when the rate of solute accumulation in the dialysis solution is zero. Peritoneal clearance is influenced by both blood and dialysate flow rates and by the MTAC. Therefore, the

maximum clearance rate can never be higher than any of these parameters. At infinite blood and dialysate flow rates, the clearance rate is equal to the MTAC and is mass-transfer–limited. Large molecular weight solutes are mass-transfer–limited; therefore, their clearance rates do not increase significantly with high dialysate flow rates. The diffusive mass transfer is estimated by Eq. (40):

$$M = I\,(A/R)\,(C_p - C_D) \tag{40}$$

Where: M = Diffusive mass transfer; A = Effective membrane surface area; I = Coefficient of proportionality; R = Sum of all resistances; C_p = Solute concentration in the potential capillary blood; and C_D = Solute concentration in the dialysate. Dividing both sides of Eq. (40) by solute concentration in peripheral blood (CB) will yield instantaneous clearance or MTAC:

$$MTAC = (M/C_B) = K = I\,(A/R)\,(\,(C_p - C_D)/C_B) \tag{41}$$

If the peritoneal capillary blood flow is infinite, C_p will be equal to C_B and we get:

$$K_i = I\,(A/R)\,(1 - (C_D/C_B)) \tag{42}$$

If the dialysate flow is also infinite, then C_D will be equal to 0, and we get:

$$K_i = K_{max} = I\,(A/R) \tag{43}$$

8.5.4 TYPES OF PERITONEAL DIALYSIS

There are two types of peritoneal dialysis: Continuous Ambulatory Peritoneal Dialysis (CAPD) and Continuous Cycling Peritoneal Dialysis (CCPD). The basic treatment is the same for each. The difference is in the number of treatments and the way the treatments are done.

a. **CAPD** is "continuous, " machine-free and done while you go about your normal activities. The treatment is done by placing about two quarts of cleansing fluid into the abdomen and later draining it. This is done by hooking up a plastic bag of cleansing fluid to the catheter. Raizing the plastic bag to shoulder level causes gravity to pull the fluid into the abdomen. When empty, the plastic bag is removed and thrown away. When an exchange (putting in and taking out the fluid) is finished, the fluid (which now has wastes removed from the blood) is drained from the abdomen and thrown away. This process usually is done three to five times a day while the patient is awake or asleep. Each exchange takes about 30 to 40 min. This technique always maintains the presence of peritoneal dialysis solution in the peritoneal cavity; it is analogous to the normal kidney function.

b. In the **CCPD** treatment, a machine (cycler) delivers and then drains the cleansing fluid for the patient. The treatment usually is done at night while sleeping.

8.5.5 ADVANTAGES AND DISADVANTAGES OF PERITONEAL DIALYSIS OVER HEMODIALSIS

8.5.5.1 ADVANTAGES

- **No need for vascular access:** This is a major advantage especially for people for whom the creation or maintenance of a well functioning vascular access

is difficult. Vascular access related complications are the most common cause of hospitalization in hemodialysis patients. Multiple access failure, either due to thrombosis or narrowing of blood vessels, is the major reason hemodialysis patients are switched to peritoneal dialysis.

- **Less dietary and fluid restriction:** Peritoneal dialysis is a continuous process of removing excess fluid and toxic material from the body, mimicking the work of native kidneys. This property of peritoneal dialysis allows patients to be less restricted in their food and fluid intake.
- **Better blood pressure control and less cardiovascular stress:** Fluid overload is the major cause of congestive heart failure and uncontrolled blood pressure in hemodialysis patients. The ups and downs of fluid accumulation and the removal of fluid by hemodialysis are also stressful to the heart. In peritoneal dialysis, there is less fluid accumulation and the removal of fluid is slow and continuous. Thus, the stress on the heart is less and blood pressure is better controlled.
- **Increased mobility:** As peritoneal dialysis is a self-administered mode of therapy, patients can adjust their treatment according to their own schedule. They do not have to go to the center; they can do their dialysis almost anywhere (car, office, home etc.).

8.5.5.2 DISADVANTAGES

- **Infection:** Peritonitis, exit site infection and tunnel infection are the major complications of peritoneal dialysis. Serious and frequent peritonitis, either due to fungal or bacterial infection, is the main reason to discontinue peritoneal dialysis and switch to hemodialysis.
- **Nutritional complications:** The combination of daily loss of protein in the peritoneal dialysate and decreased capacity to intake food due to increased intraabdominal pressure, protein energy malnutrition has been observed in some peritoneal dialysis patients. Hyperlipidemia (increased cholesterol and triglyceride levels) has also been observed in these patients, especially during the initial period of treatment, and is due to high peritoneal glucose load. This high glucose load also causes excessive weight gain in these patients.
- **Chronic back pain and hernia:** Increased intraabdominal pressure secondary to peritoneal fluid can cause chronic back pain and/or abdominal hernia in some patients.

8.5.6 COSTS OF DIALYSIS

The cost to the patient for all types of dialysis depends on the condition of a patient, location of a hospital/dialysis center in a particular country, aid or subsidy by a government/nonprofit organizations, insurance company, in-center or at home treatment, frequency of dialysis, postdialysis medication and nutritious diet to compensate the general weakness caused by the treatment, and economic status of a patient. This does not include costs due to increase in monthly bills for utilities, visits to the doctor's office, laboratory/X-ray, and medicine. In some locations around the world, the patient may have to make the copayment after the fixed percentage of a total cost is covered by an agency. Dialysis costs are around $50,000 to $100,000 per year. The patient can

opt for in-center or at-home dialysis treatment. The reader is highly recommended to consult the article titled, "Bulgin, Roy H., 1980. *Comparative Costs of Dialysis Treatments.* Peritoneal Dialysis International, Toronto Western Hospital- Canada." The results of this study are summarized as follows: "*The total costs -supplies, salaries and other "direct" costs were calculated for in-center intermittent peritoneal dialysis (IPD), home peritoneal dialysis (CAPD and IPD) and in-center hemodialysis (assisted and self-care), all of which are provided at the Toronto Western Hospital. For the costs of home hemodialysis, for comparison purposes, he used data obtained from the Toronto General Hospital. The average costs (in Canadian dollars) per patient year, not including any medical fees, were: In-center intermittent peritoneal dialysis: $31,536; Home IPD: $21,600; CAPD: $12,360; Incenter assisted hemodialysis (with three times (average) dialyzer reuse): $18,048; self-care hemodialysis (with three times (average) dialyzer reuse and using the hospital's equipment): $13,752; and home hemodialysis (with limited dialyzer reuse): $13,116."* These costs were calculated by Dr. Roy H Bulgin, Associate Director at Toronto Western Hospital – Canada, for the fiscal year April 1 of 1979 to March 31 of 1980. Table 5 summarizes the typical cost per patient per month. The economist can use this article as a guide to calculate a typical cost of a treatment.

TABLE 5 Comparison of average cost (Canadian $ per patient per month) of dialysis for three units in 1980: Toronto Western Hospital. **Note:** in-center intermittent peritoneal dialysis = **IPD** and home care peritoneal dialysis = **CAPD**. <http://pdiconnect.com/content (1)6/88.full.pdf>

Average cost for	Average cost per patient month, Canadian $	Average cost per patient year, Canadian $
In-center peritoneal dialysis	2,628	31,536
In-center hemodialysis (includes both assisted and self care hemodialysis) **	1,424	17,088
Home peritoneal dialysis (includes both CAPD and IPD)	1,069	12,828
Calculated cost for:		
Home IPD*	1,800	21,600
Home CAPD	1,030	12,360
Self-care hemodialysis***	1,146	13,752
Hospital hemodialysis**	1,504	18,048
Home hemodialysis****	1,093	13,116

*Estimated costs.

**With three times (average) dialyzer reuse.

***Performed with hospital facilities and with three times (average) dialyzer reuse.

****Data from the Toronto General Hospital (with limited dialyzer reuse).

The typical costs are listed below as a guide:

- Dialysis is covered by health insurance of a patient. For patients covered by health insurance, out-of-pocket costs typically include the deductible, and coinsurance for the treatment cost. For example in USA with Medicare, once the deductible of is met, a patient typically would pay coinsurance of 20%; but many Medicare patients also have secondary insurance to cover all or part of that cost. A study published in Health Affairs showed that the average U.S. patient pays **$114** for dialysis-related drug costs and about **$10** in dialysis costs per month.
- For patients not covered by health insurance, a single hemodialysis treatment typically costs up to **$500** or more – or, about **$72,000** or more per year for the typical three treatments per week. Injectable medications and vitamins can add hundreds of dollars to the cost, depending on what is prescribed. For example, DaVita, which has many dialysis centers across the United States, charges about **$480** for a dialysis treatment, not including medications. A dialysis center in Ohio quotes a rate of more than **$1,400** but will negotiate with self-pay patients.
- An emergency, unscheduled dialysis treatment at a hospital can cost much more; for example, Baptist Memorial Health Care in Memphis charges about **$9,900** for a single treatment. For peritoneal dialysis, the main costs consist of medical supplies to perform the procedure at home – so it is slightly less expensive than hemodialysis. According to the U.S. Renal Data System, one year of hemodialysis can total **$72,000**; a year of peritoneal dialysis can cost about **$53,000**.
- Most patients with end-stage renal disease are eligible for Medicare; however, the typical waiting period is about four months before the coverage starts (or, if the patient is insured through an employer group health plan, that plan will be the primary payer for 30 months). <medicare.gov> has information on medicare and end-stage renal disease. Medicare Part B, which is necessary to get dialysis benefits, costs more than **$100** per month.
- <http://www.kaycircle.com/Average-Cost-of-Kidney-Dialysis-2011> indicates that the average cost of kidney dialysis in 2011 was $100,000.
- **Additional costs:** Hemodialysis requires surgery to create vascular access, while peritoneal dialysis requires surgery to insert a catheter in the abdomen. According to the "U.S. Renal Data System," these costs can range from about **$1,000** to **$7,500** or more. For hemodialysis at home, special plumbing and wiring will need to be added for about **$1,250–$2,000,** according to the "American Association of Kidney Patients." Dialysis patients need to follow a special diet under the guidance of a dietician. "The National Kidney and Urologic Diseases Clearing house" offers a primer on dialysis and diet. Many hospitals have dieticians available. The initial consultation for the dietician can cost **$100–$200**.
- **General:** In continuous peritoneal dialysis, which typically is done several times per day or at night by a machine, a cleansing solution is pumped via a catheter into the abdomen. A membrane in the abdomen draws wastes, excess sodium and fluids into the solution, which is then drained out of the body. The process must be repeated several times per day or continuously at night. In hemodialysis, which typically is done three or more times per week, the patient sits in a

reclining chair as the blood is removed and run through a filter in a machine, then returned to the body. The National Institutes of Health has overviews of peritoneal dialysis and hemodialysis: <kidney.niddk.nih.gov/kudiseases/pubs/hemodialysis/>hemodialysis>. "The American Association of Kidney Patients" has an article on home hemodialysis. "Dialysis provider DaVita" offers a primer on dialysis drugs and vitamins.

- **Comments:** In May of 2010, there were more than 350,000 Americans receiving dialysis. Medicare in USA pays billions of dollars every year for dialysis treatments, medications, and hospitalizations of patients with ESRD (end stage renal disease). For more information on "Annual Cost of Dialysis Treatment," one may consult at: <http://www.ehow.com/about_6582885_annual-cost-dialysis-treatment.html#ixzz2A43wuP7C>

8.5.7 WHARTON AND STANFORD STUDY <HTTP://KNOWLEDGE.WHARTON.UPENN.EDU/ARTICLE.CFM?ARTICLEID=1949>

Wharton and Stanford study estimated the cost treatment in 2008 for about $129,000 per each qualitative year. This study indicated the step down cost of $61,000-$65,000. The cost for home nocturnal hemodialysis was about $55,139 +/– $7,651 than for in-center hemodialysis $66,367 +/– $17,502. "American Association of Kidney Patients, <www.aakp.org>" indicates $30,000 per year for the out of pocket cost to the patient, after the affiliated are covered by medicare or Medicaid or an insurance company. AAKP estimates do not include the initial set-up costs of about $2,000–2,500 for back-flow preventers on the plumbing lines, waste (drain) lines and the installation of a dedicated 20 amp receptacle. The usefulf weblnks are:

<http://www.kidneyfund.org/patient-programs/>
<www.kidney.org>
<www.homedialysis.org>
<www.smh.com.au/natinal>

8.5.8 CLINICAL RESULTS

Many patients prefer in-home treatment since it can be done at home with the help of a family member. It lets them go about daily activities. The main problem associated with CAPD is the development of peritonitis. Peritonitis is caused when there is an infusion of bacteria into the cavity. If recognized at an early stage, it can be treated with antibiotics but a new catheter has to be in placed.

8.6 PERITONEAL DIALYSIS EXCHANGE DEVICE

The Freedom CyclerPD (Appendix 1) device is used in this chapter only to explain the operation. The reader is advised to consult the operator's manual for a specific make and model. All makes/models are not same. The Freedom CyclePD device consists of control unit, a base stand, and a lower valve.

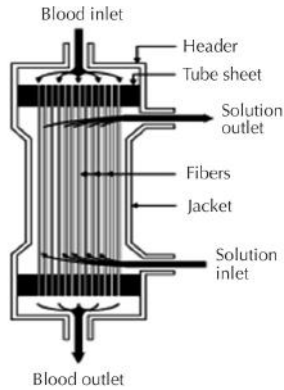

FIGURE 11 Structure of typical hollow fiber dialyzer (8).

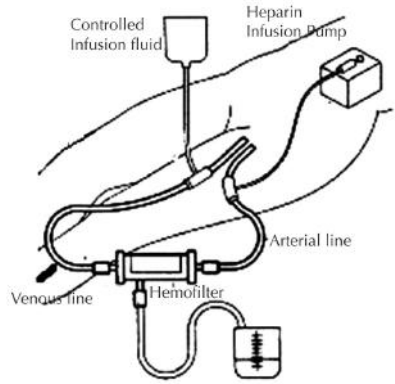

FIGURE 12 Continuous arteriovenous hemoflitration.

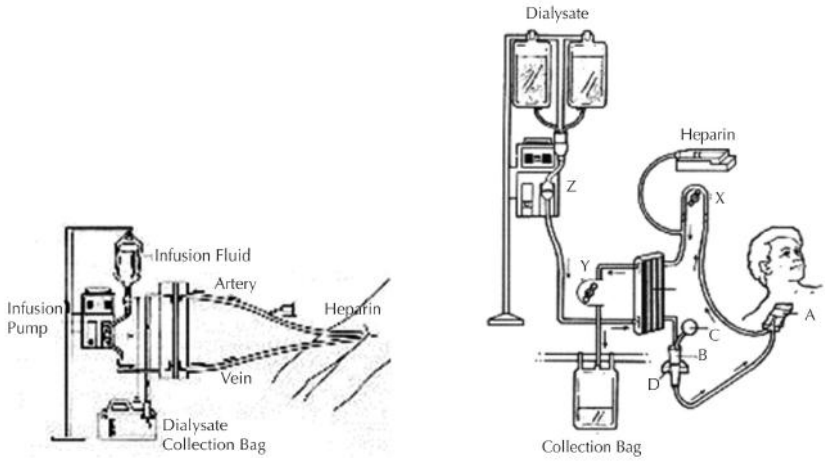

FIGURE 13 Continuous venovenous hemodialysis (7): A = double-lumen subclavian vein access; B = venous air trap; C = venous pressure monitor; D = air detector; E = dialyzer; *x*, *y*, z = blood and dialysate pumps.

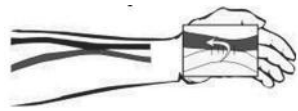

FIGURE 14 Arterio-venous fistula: connection of an artery and a vein (18).

FIGURE 15 Arterio-venous graft: tubing connected to the artery.

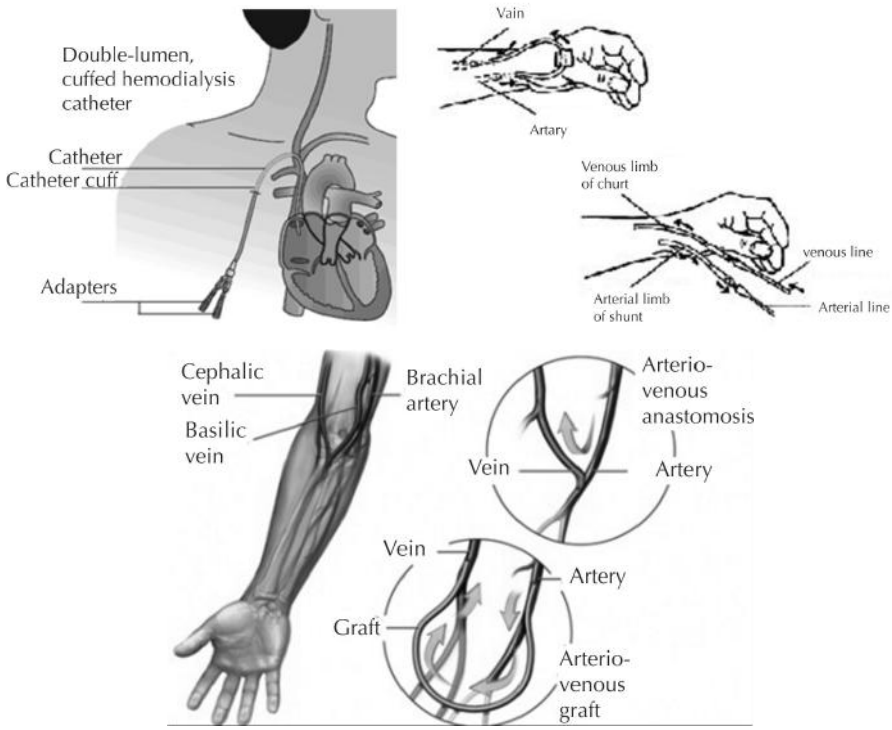

FIGURE 16 Venous catheter for temporary hemodialysis
Access: subclavian vein access (left top); Wrist (Right top); Arm (Bottom)

The control unit consists of a control panel, a heater – scale, and an upper valve. The heating – scale unit, warms and weighs the dialysate bags. The front control panel has five keypads and a display screen. All messages for treatments, ajustments and pogramation are displayed on the screen. With the use of the five keypads: (START), (STOP), (SELECT), and the "UP" and "DOWN" arrow keys, the patient can program the desired treatment.

The (START) keypad is used to advance through the different phases of the treatment. It is also used to continue operation in case an alarm goes off. The (STOP) keypad is used to mute the alarm or interrupt the treatment. The (SELECT) keypad and "UP and "DOWN" arrow keys are used to change and select the desired program.

The lower valve is located on the stand base and it plugs into the cycler control unit. The lower valve's job is to drain the patient and to weigh the bag.

The device allows the patient to make desirable adjustments. Some of the options that can be adjusted are: The number of changes (infusions); The number of pauses between infusions; Volume of pause; Volume DPCC; Volume of last infusion; Total Volume; Infusion time; Permanence time; Drainage time; Preheating; Type of treatment; and the desired language.

8.6.1 TYPES OF TREATMENT

There are four types of treatments available in Freedom CyclerPD: PD-Plus Therapy, Peritoneal Dialysis Continued Cycle (PDCC), Intermittent Peritoneal Dialysis (IPD), and Tidal Peritoneal Dialysis (TPD).

In the **PD Plus therapy**, the dialysate is maintain in the peritoneum during the day. This means that toxic wastes and liquids are being removed continually. This treatment will provide for a new dialysate for the changes during the day and at night.

With **PDCC,** the dialysate is maintained in the peritoneum the whole day but changes are only made during the night while the patient is asleep. There are no changes during the day, when the patient connects to the cycler he or she has to drain the dialysate that has been in the peritoneum during the day.

The **IPD** is a therapy that is interrupted or intermittent. The patient receives the changes of dialysate during the night, while sleeping, but will not have dialysate in the peritoneum during the day.

The difference with the **Tidal treatment** is that after the initial infusion, only part of the dialysate is drained, never allowing the peritoneum to be empty.

8.6.2 MAINTENANCE

The maintenance of the device should be done by a qualified person. The surface of the Cycler should be cleaned after each treatment using a wet cloth and a dilute solution (1:1000) of a surface disinfectant.

8.7 HEMODIALYSIS

The hemodialysis is the most common method to treat advanced and permanent kidney failure. Since the 1960s, when hemodialysis first became a practical treatment for kidney failure, much advancement has been made to make the treatment more effective and minimize side effects. The treatment involves circulating the patient's blood outside of the body through an extracorporeal circuit (ECC) or dialysis circuit. Two needles are inserted into the patient's vein or access site, and are attached to the ECC. The ECC consists of plastic blood tubing, a filter known as a dialyzer (artificial kidney), and a dialysis machine that monitors and maintains blood flow and administers dialysate. Since the 1980s, the majority of hemodialysis treatments in the United States have been performed with hollow fiber dialyzers (Fig. 11). A hollow fiber dia-

lyzer is composed of thousands of tube-like hollow fiber strands encased in a clear plastic cylinder several inches in diameter. There are two compartments within the dialyzer: the blood compartment and the dialysate compartment. The membrane that separates these two compartments is semipermeable; it works like a peritoneal membrane. It allows the small molecules to pass, but holds back the larger molecules. As blood is pushed through the blood compartment in one direction, suction or vacuum pressure pulls the dialysate through the dialysate compartment in the opposite direction. These opposing pressures work to drain excess fluids out of the bloodstream and into the dialysate, this process is called ultrafiltration. Waste products in the blood are moved across the membrane and into the dialysate compartment, out of the body, by diffusion. While this is happening, electrolytes and other chemicals in the dialysate solution cross the membrane into the blood compartment. The purified, chemically balanced blood is then returned to the body.

Most hemodialysis treatments are done for an average of three to four hours, three times a week. These are done in a hospital or a dialysis center.

8.7.1 CONTINUOUS ARTERIOVENOUS HEMOFILTRATION (CAVH)

In this process blood circulates through a small hollow fiber hemofilter, with or without the use of a blood pump. The access to the circulatory system is by the femoral artery and vein. Heparin is infused continuously at the same the hemofilter wherein the plasma and collected in the collection bag. Replacement fluid is infused into the venous return line (Fig. 12).

8.7.2 CONTINUOUS VENOVENOUS HEMOFLITRATION (CVVH)

This therapy involves the assistance of a pump, thus achieving greater effectiveness. The blood access is achieved by placing a double lumen catheter in the internal jugular vein. Continuous diffusive solute transport is achieved by infusing a dialysis fluid that runs at the same time but in opposite direction to the blood at a flow rate of 15 mL/min or 1 L/hr. CVVH is shown in Fig. 13.

8.7.3 CONTINUOUS ARTERIOVENOUS HEMODIALYSIS (CAVHD)

The use of an infusion pump, hemodialysis membrane and dialysate solution is necessary for this type of therapy. It uses the same blood access circuitry as the CAVH technique. A continuous drop of dialysis fluid is pump by an infusion pump into the dialysate compartment of a hemodialyzer membrane. This therapy uses the process of continuous diffusion dialysis to get rid of the body's fluids, electrolytes, and nitrogenous wastes. The access site normally used is the femoral artery (Fig. 14).

8.7.4 CONTINUOUS VENOVENOUS HEMODIALYSIS (CVVHD)

This technique uses the same blood access circuitry as the CVVH technique; it also uses an infusion pump, hemodialysis membrane and dialysate solution. Like the CAVHD technique, in CVVHD the adding of the dialysis membrane and the dialysate solution increases the efficiency of the procedure. Because the low pressure venous system does not filter as much blood per unit of time, this process is less effective than that of the CAVHD (Figs. 12 to 14).

8.8 VASCULAR ACCESS

A vascular access is a connection of an artery and a vein in the body to let the blood be removed and returned to the body during the hemodialysis treatment. For hemodialysis blood must be removed from the body, passed through a dialyzer and returned. Since it may be necessary to make and break these connections several times a week, various methods have been developed for inserting tubes into blood vessels. These methods are better known as vascular accesses.

8.8.1 TYPES OF VASCULAR ACCESSES (FIGS. 14 TO 16)

There are three main kinds of vascular accesses: the arterio-venous fistula; the arterio-venous graft; and temporary access.

a. The Arterio-Venous Fistula is the surgical connection of an artery directly to a vein, allowing more blood to flow into the vein (Fig. 15). This kind of access takes a while after surgery to develop, but with proper exercise in about six to eight weeks veins develop and become enlarged and stronger to make easy access for the hemodialysis treatment. The fistula is less likely than the other kind of accesses to form clots or become infected. And it tends to last many years, longer than any other kind of vascular access.

b. The Arterio-Venous Graft is man-made synthetic tubing that is surgically connected to the artery and the vein (Fig. 14). The graft is used when the patient has small veins that will not develop into a fistula. It is located close to the surface of the skin to make easier the needle insertion process. Grafts are most commonly placed in the upper arm, lower arm, and thigh. The graft may be either straight or looped, and can be either made of an artificial material or obtained from the patient's own body using another vein. The graft doesn't have to develop like a fistula, so it can usually be used in about two to four weeks.

In some cases, as when urgent dialysis is needed and the patient cannot wait weeks for the fistula to be ready for use, catheters must be used as temporary accesses (Fig. 15). These include the subclavian catheter, the internal jugular catheter and the arterio-venous shunt (Fig. 16).

The subclavian catheter is a tube that is inserted into the subclavian vein near the neck, while the internal jugular catheter is placed in the veins by the side of the neck. The jugular catheter, when used further than a few weeks, tends to get blocked by clotting blood or by infection on the site of insertion. The arterio-venous shunt is surgically created and consists of two pieces of tubing, each with a Teflon tip on one end. The tips are placed one in an artery and the other in an adjacent vein. Due to clotting or infection the arterio-venous shunt has limited duration. In fact it does not work for more than six months.

8.8.2 COMPLICATIONS DURING HEMODIALYSIS

Although much advancement has been made to improve the technology of hemodialysis, the patient is still at some risk for some side effects and/or complications. These complications are:

1. **Anemia** – Hematocrit (Hct) levels, a measure of red blood cells, are typically low in patients. This deficiency is caused by a lack of the hormone erythro-

poietin, which is normally produced by the kidneys. The problem is elevated in hemodialysis patients, who may incur blood loss during hemodialysis treatments. Epoetin alfa, or EPO (sold under the trade name Epogen), a hormone therapy, and intravenous or oral iron supplements are used to manage anemia in dialysis patients.

2. **Cramps, Nausea, Vomiting, and Headaches** – Some hemodialysis patients experience cramps and flu-like symptoms during treatment. Some of the factor that can caused this are: the type of dialysate used, composition of the dialyzer membrane, water quality in the dialysis unit, and the ultrafiltration rate of the treatment. An adjustment to the dialysis prescription often helps alleviate many symptoms.
3. **Hypotension** – Because of the stress placed on the cardiovascular system with regular hemodialysis treatments, patients are at risk for hypotension, a sudden drop in blood pressure. This can often be controlled by medication and adjustment of the patient's dialysis prescription.
4. **Infection –** Both hemodialysis and peritoneal dialysis patients are at risk for infection. Hemodialysis patients should keep their access sites clean and watch for signs of redness and warmth that could indicate infection. Peritoneal dialysis patients must follow the same precautions with their catheter. Peritonitis, an infection of the peritoneum, causes flu-like symptoms and can disrupt dialysis treatments if not caught early.
5. **Infectious diseases** – Because there is a great deal of blood exposure involved in dialysis treatment, a slight risk of contracting hepatitis B and hepatitis C exists. The hepatitis B vaccination is recommended for most hemodialysis patients. As of 1997, there has only been one documented case of HIV being transmitted in a United States dialysis unit to a staff member, and no documented cases of HIV ever being transmitted between dialysis patients in the United States. The strict standards of infection control practiced in modern hemodialysis units make the chance of contracting one of these diseases very small.

8.8.3 HEMODIALYSIS PROCEDURE

The type of hemodialysis treatment is selected by the patient and his doctor. The doctor will instruct the patient and fill out an order form with the following information: Type of dialysis; Dialyzer; Blood flow rate; Dialysate composition; Frequency and duration; Estimated ideal or dry weight and amount of fluid to remove as well as blood pressure support; Nutritional management including fluid intake; Laboratory tests before and after dialysis: electrolytes, creatinine, calcium, phosphates, glucose, total bilirubin, cholesterol, total protein, albumin, and total blood count; and Medication to be given during the treatment.

8.4 HEMODIALYSIS CONTROL UNIT

8.4.1 THE BASIC SYSTEM

Here we will discuss a typical hemodialysis control unit. Every manufacturer will have its own specifications. For more details, the reader should consult the "Operator's

Manual for Gambler Cobe CenturySystem3 (Dialysis Control Unit) that is a totally self-contained machine < www.gambro.com/en/global/>." Basic functions of the unit are:

- Automatically primes extracorporeal circuit.
- Prepares dialysate.
- Monitors dialysate and blood.
- Pumps blood and anticoagulant at predetermined rates.
- Controls fluid removal.
- Automatically cleans, disinfects, and rinses dialysate flow path.

A video display screen and the main operator control push buttons are located on the upper front of the machine. The operating status during dialysis and information to help the operator in setting up the machine are shown on the screen. Using the buttons and the screen, the operator can select the operating parameters-acetate or bicarbonate; optional single needle dialysis; the heparin rate, infusion time, and bolus amount; the temperature of the dialysate; the concentration of sodium in the dialysate at one level or an optional two or three levels; and monitoring information. The ultrafiltration system of the unit safely and efficiently controls fluid removal during dialysis. Using the display screen and the adjacent buttons, the operator enters the specific length of time for individual dialysis procedure and the desired amount of fluid to be removed. The unit then automatically determines and maintains the correct ultrafiltration rate throughout the treatment to achieve the specified fluid removal value.

In addition to assisting the operator in setting up and monitoring dialysis, the display screen is also part of the alarm system. If alarm or cautionary conditions occur, the operator is alerted in three ways: An audible alarm; A flashing red or yellow central alarm light; and an alarm message on the display screen.

Controls for priming and blood pump operation are located adjacent to the blood pump. The specially designed COBE Cartridge set is easy to install on the machine. The COBE Cartridge set allows noninvasive prepump arterial and venous pressure monitoring and eliminates the need for transducer protectors. Flexible diaphragms on the back of the COBE Cartridge set provide the direct interface with the machine. When the extracorporeal circuit is set up, the machine controls automatic priming of the circuit.

During the dialysis, the machine proportions concentrate with heated deaerated water to the specified ionic content for dialysis. The dialysate solution is continuously monitored and controlled for temperature and conductivity. It is also monitored for the presence of blood. The pH level of the dialysate is monitored too. If temperature, conductivity, or pH reach unsafe levels, the machine automatically diverts unsafe dialysate from circulating through the dialyzer. The appropriate alarm indicators (audible and visual) alert the operator to unsafe conditions. If blood is detected in the dialysate: the blood pump stops, the venous line clamp stops flow through the venous blood line, and audible and visual indicators alert the operator.

The operator determines the rate at which blood is pumped from the patient and the rate at which heparin is infused into the blood circuit. The blood is monitored for the presence of air. The pressure in the blood lines is monitored at the COBE Cartridge set. If the air bubble detector detects air or pressure changes exceed specification, the

blood pump stops and the venous line is also automatically clamped. Audible and visual alarm indicators alert the operator to these conditions.

If the power fails during operation, a steady audible alarm sounds. If the water supply fails, an audible alarm sounds, the red central light illuminates, a message appears on the display screen, and the heater shuts off.

Another feature of the unit is automatic clean, disinfect, and rinse (ACDR) which minimizes the handling of chemicals. Two large chemical containers (approximately one week's supply) or chemicals in their original packaging are connected to ports on the rear of the machine- one for cleaning and one for disinfecting. The operator is required only to activate the ACDR softkey and move either the acetate or the bicarbonate concentrate line to a chemical port on the front of the machine. The acetate concentrate line is connected for the clean cycle, and the bicarbonate concentrate line is connected for disinfect cycle. The machine draws the appropriate amount of chemical, dwells it in the machine if necessary, rinses it out, and then turns off the water and power to all the pumps.

8.4.2 OPTIONAL FEATURES

a. Programmable Sodium (Na+)

This option allows the selection of three additional operating parameters:

1. Two or three sodium levels during procedure (130 mEq/L to 160 mEq/L).
2. Time spent at each level (not to exceed selected dialysis TIME LEFT).
3. Rapid or gradual change from one level to the next.

b. Single Needle (SN)

Another available option is the SN option, which controls on and off cycling of the blood pump to provide blood flow through a single needle access (Y-flow single lumen needle or catheter). In the arterial phase of the cycle, the arterial line is unclamped, the venous line is clamped, and the blood is pumped from the patient until the pressure reaches the venous pressure high trip point. When the pressure reaches this point, the machine switches to the venous phase. The blood pump is stopped, the venous line is unclamped, the arterial line is clamped, and as blood is returned to the patient, the venous pressure falls until it reaches the venous pressure low trip point and the cycle begins again. The COBE Cartridge set specially designed for single needle dialysis has all the features of the set designed for double needle dialysis. In addition, the SN set has two pumping chambers (predialyzer and postdialyzer) that provide stroke volume capacity without needing level adjustments.

c. Centry Charts (CC)

The Centry Charts option with or without the Centry BP option is available as a software adaptation for the unit, allowing the clinician to automatically record machine treatment data on electronic charts. When installed in the machine, CC is displayed on the options screen and may be accessed with the new charts/bp button on the control panel. CC option allows the operator to select automatic timed intervals for collecting machine data, which can be easily monitored throughout the dialysis treatment. From the charts on the screen, the operator can view the following data:

- Monitored ultrafiltration rate.
- Amount of fluid that has been removed.
- Monitored arterial machine pressure.
- Monitored venous machine pressure.
- Blood pump speed.
- Monitored transmembrane pressure.
- Final conductivity of the machine.
- Monitored temperature of the dialysate.
- Sodium level.
- Stroke volume for Single Needle.
- Average blood flow rate for Single Needle.
- Cumulative liters processed.

From the Main charts/bp screen, additionally, the amount of time left in a treatment and the amount of time dialyzed is displayed for review.

d. Blood pressure monitor (BP)

With the Centry BP option to the CC, the clinician has the capability of monitoring and collecting patient as well as machine data. The Centry BP option, when present in the machine, will be displayed on the options screen and is accessed with the charts/bp button on the control panel of the unit.

The technology of the Centry BP option was developed for use in noninvasive blood pressure monitoring and compares favorably to the manual method of registering blood pressure readings. In spite of the favorable comparison, the Centry BP option may display blood pressure measurements that are not clinically accurate for a small percentage of hemodialysis patients. This phenomenon may be related to the specific cardiovascular pathology of some hemodialysis patients. Some hemodialysis patients may also have previously used blood access sites that have altered their vascular structure, causing this phenomenon in blood pressure measurement. Therefore, the decision to use the Centry BP option on certain hemodialysis patients should be made following good medical judgment and clinic protocols.

The Centry BP option consists of an electronic module located inside the unit and a fabric blood pressure cuff connected to the module by a tube. There are two openings on the lower edge of the cuff from which the tubing may protrude, allowing the cuff to be used for either arm. The cuff is available in sizes ranging from child to large adult, and a thigh cuff is also available for patients with poor upper torso circulation. Two stick Figures with either the right or left arm extended mark these openings on the outside of the cuff. An arrow designated with the letters “ART” appears on the lower edge of the cuff, assisting in the placement of the cuff over the patient’s upper brachial artery.

The CC and the BP options, provide a sophisticated way to monitor patient vital signs and important treatment data during each dialysis treatment.

e. BiCart (Bi)

By installing the BiCart option on the unit, the clinician has the ability to perform bicarbonate dialysis with on-line production of liquid bicarbonate concentrate in lieu of connecting bicarbonate jugs. Two components are necessary in order to perform

BiCart. Column is a polypropylene column containing sodium bicarbonate powder. This column, fitted into a special holder that is attached to the unit, enables the on-line production of bicarbonate concentrate. BiCart and bicarbonate jug dialysis are not to be performed simultaneously.

When the BiCart column is attached to this special holder, fluid will be drawn from the unit through the BiCart column, thus producing a saturated solution of sodium bicarbonate. The bicarbonate proportioning system in the unit proportions this solution. The unit mixes the solution with heated water and acid concentrate to produce a bicarbonate dialysis fluid.

f. CentryNet

The CentryNet network controller offers the clinician a new type of optional enhancement for the dialysis control unit. The CentryNet controller, though not affecting the outcome of dialysis therapy, does simplify and automate the clinician's record keeping task by collecting treatment-related data through a computerized network of units. Understanding the CentryNet controller involves understanding what the CentryNet controller does, how it performs, how it communicates, and how collection of treatment data is ended when using the CentryNet controller.

With the CentryNet option, units are cabled together for communication with a network controller. The network controller is a specially conFigured personal computer that collects and sorts data. The operator can perform four basic tasks at the unit, such as:

- Verifying the physical location of the unit (station ID as conFigured on the Centry Net option).
- Entering a unique patient id for each patient receiving a treatment.
- Pressing the start treatment softkey on the unit to start data collection for a treatment.
- Pressing the end treatment softkey on the unit to end data collection for a treatment.

When the unit is between treatments: the CentryNet controller collects no treatment data. Therefore, the operator should remember not to perform any therapy-related, data-generating tasks between treatments. If for any reason the operator does not press the start and end treatment softkeys on the unit in the required sequence and data collection is interrupted for any mechanical reason, the treatment data collection will be prematurely concluded. The CentryNet collected data for such a treatment will be incomplete. After the operator presses the start treatment softkey, data are collected (as taken) for the following information:

- Any machine setup parameters, e.g., at start treatment and whenever the machine enters dialyze.
- All charts/bp data.
- Any changes that may occur in the machine setup, if specified in the configuration for data collection on the CentryNet controller.
- All machine status changes, i.e., when a unit goes online or offline, when a network goes online or offline, or when the CentryNet controller is started up or shut down.

During the dialysis treatment, the CentryNet controller automatically collects data without operator assistance or intervention. When the operator presses the end treatment

softkey, the CentryNet controller stops collecting data for that treatment. The treatment is summarized and "closed out" on the network controller.

8.4.3 COMPONENTS OF THE CENTRYNET UNIT

a. Front Panel (Fig. 17)

The front panel is divided into three sections. The upper section consists of the central alarm lights and the communications module with its display screen and operator pushbuttons. The blood handling portion of the machine is located directly below the communications module. The blood pump and its control panel, dialysate hoses, dialyzer holder, blood set cartridge holder, air bubble detector, venous line clamp, arterial line holder, and heparin pump are located there. The chemical ports, concentrate connectors, and rinse ports are located on the lower section of the front panel. The BiCart option is also located on the lower front panel. For convenience, the concentrate containers can be placed on the front shelf. The following front panel components for the machine are shown as numbers in Fig. 17:

1. I.V. Pole: The I.V. pole is adjustable.
2. Central Alarm Lights: a. *Green central safe light* – When this steady light is on, the machine has no existing cautionary or alarm conditions and is in the dialyze mode; b. *Yellow central caution light* – The flashing yellow central caution light, which is accompanied by an audible alarm, indicates that the operator should be aware of particular operating conditions. The steady yellow light indicates there are no existing caution conditions and the machine is in the setup, recirculate, or rinseback mode; and *Red central alarm light* – The flashing red central alarm light, with the audible alarm, indicates that an abnormal condition exists which requires prompt operator attention Unless the condition is corrected, patient safety may be compromised. The steady red light indicates there are no alarms present and the machine is in the calibration or ACDR mode.
3. Communications Module: The communications module is composed of video display screen and the main operator control pushbuttons. In addition to assisting the operator in setting up and monitoring dialysis, the display screen is part of the alarm system.
4. Blood Pump Control Panel: The blood pump control panel contains the pump controls and flow rate display.
5. Power Switch: This switch turns the power on and off to the machine. It is labeled "1″(on) and "0″(off). The "0″ does not have to remain depressed for the machine to be off.
6. Dialysate From Dialyzer Hose (color coded red): This hose removes used dialysate from the dialyzer. During dialysis, it connects to the dialysate outlet port on the dialyzer. During cleaning, disinfection, rinse, or storage, this line is connected to the upper bypass port.
7. Filter Screen: This 158-micron screen traps particulates and protects the internal hydraulics downstream of the dialyzer.

8. Dyalisate To Dialyzer Hose (color coded blue): This hose transports dialysate to the dialyzer. During dialysis, it connects to the dialysate inlet port on the dialyzer. During cleaning, disinfection, rinse, or storage, this line is connected to the lower bypass port.
9. Sample Port/Pressure Vent: Using a syringe, a sample ofthe incoming dialysate can be withdrawn from the sample port. The final conductivity should be checked before dialysis in either an acetate or bicarbonate procedure. This port also allows excess pressure to be vented from the To Dialyzer hose.
10. Bypass Ports (To Dialyzer and From): Dialyzer hoses are connected to these ports, when the machine is being cleaned, disinfected, or rinsed. The dialyzer hoses can also be connected to these ports for storage or when the hoses are not required to be connected to the dialyzer. A switch that senses when the hoses are connected is built into these ports. It is important that the flanges on the dialysate hose connectors be snapped forward to ensure that the switch is activated.
11. Dialyzer Holder: This holder secures a hollow fiber dialyzer in place. An accessory holder is required for parallel plate dialyzers.

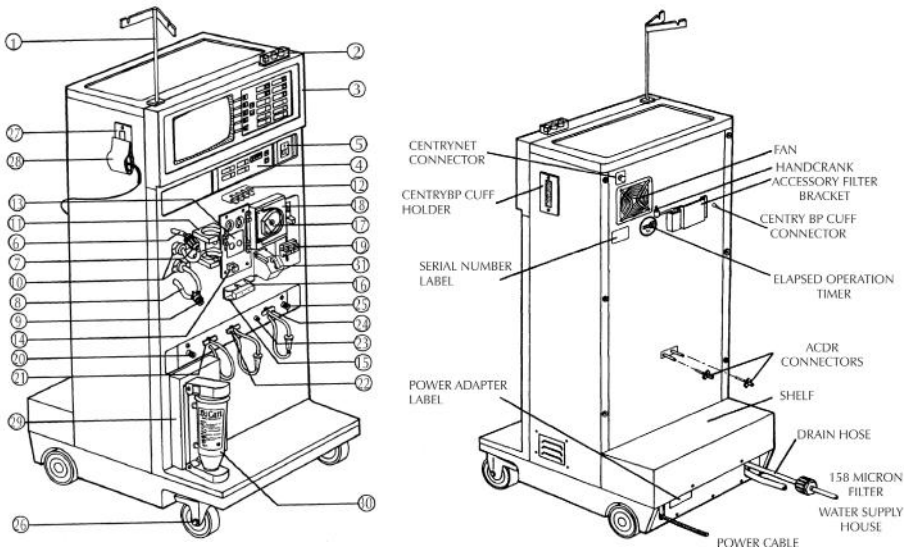

FIGURE 17 Freedom Cycler: Operator's Manual for the COBE Centrysystem 3 Dialysis Control Unit by GAMBRO Renal Care Products Inc. **Left**: Front panel unit; **Right**: Rear panel unit.

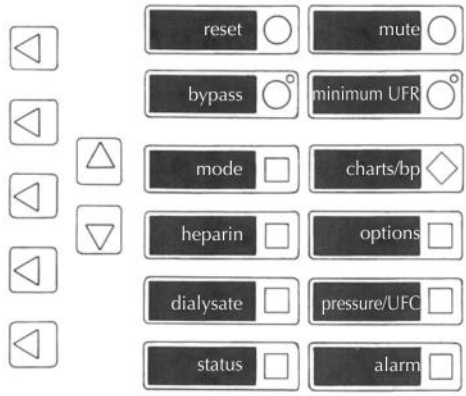

FIGURE 18 CentrySystem 3 dialysis control unit: Control panel (Gambro 2000).

TABLE 5 Maintenance After Each Dialysis (Gambro 2000).

Interval	Precipitate Control/ Rinsing	Cleaning	Disinfection
After each dialysis	—	Exterior cleaning	Exterior disinfection
Daily	Vinegar/acid rinse or Citric acid rinse	Flow path cleaning	Flow path disinfection
Weekly	Nitric acid rinse Citric acid rinse	Clean dialysate hose connector Clean filter screens	Flow path disinfection

12. Four-Position Access Line Clamp: This is a 4-line clamp, holding (from right to left) the heparin line, arterialaccess line, cartridge saline line, and the venous access line from the cartridge. The desired line is clamped by turning the appropriate knob horizontally.
13. COBE Cartridge Holder: This holder secures the COBE Cartridge set onto the front panel. Two pressure monitoring sensors engage the back of the COBE Cartridge set when the load/unload button is pressed to close the blood pump cover.
14. Air Bubble Detector: This ultrasonic sensor detects air in blood or saline. When air is detected, the blood pump stops and the venous line clamp closes, preventing further blood flow to the patient.
15. Venous Line Clamp: The venous line clamp is an electronically activated device that closes the venous blood line when blood is detected in the dialysate, when air is detected in the venous blood line, and when various other alarms occur. For SN Option only, the venous line clamp is closed during the arterial phase. This prevents blood from returning to the patient or from being shunted

back into the arterial blood line. During the venous phase, the venous line clamp is open to allow blood to flow back to the patient.

16. Arterial Line Holder/Arterial Line Clamp: This holdersecures the arterial line in place. The arterial line clamp is available for SN Option only. The arterial line clamp is open during the arterial phase to draw blood into the extracorporeal circuit. During the venous phase, the arterial line clamp is closed to prevent dialyzed blood from being shunted back into the arterial blood line.
17. Blood Pump and Blood Pump Cover: The pump circulates blood through the system. It is a self-occluding, spring-loaded pump that provides even pressure to compensate for variations in tubing dimensions. When the load/unload button is pressed on the blood pump control panel, the cover opens approximately ½ inch enough space to slide the COBE cartridge pump segment inside. While the cover is open, the blood pump will not run. When the load/unload button is pressed again, the cover closes and the pump rotates to thread the pump segment onto the pump. While the cover is closed, the blood pump can run, occluding the pump segment. The pump is easily cleaned by pressing the load/unload button to open the cover. Pressing the latching pin on the top of the clear, plastic cover door allows the door to swing open so that the pump raceway can be reached for cleaning. When the door is closed, the latching pin locks it in place.
18. Syringe Holder: This holder secures a 10,12, or 20 cc syringe containing heparin.
19. Plunger Clamp: This clamp is motor driven upward to automatically infuse heparin.
20. Chemical Port: During the clean cycle, the acetate concentrate line is concentrate line is connected to this yellow chemical port.
21. Acetate Concentrate Line and Rinse Port: This concentrate line connects to the acetate concentrate container when the machine is operated for an acetate procedure. The connector on the end of this line and its associated rinse port are color-coded white on a CE-Marked machine and brown on a non CE-Marked machine, and are uniquely sized to prevent misconnection. During rinse, storage, or when the machine is operated for a bicarbonate procedure, this line is connected to its rinse port.
22. Acid Concentrate Line and Rinse Port: This concentrate line connects to the acid concentrate container when the machine is operated for a bicarbonate procedure. The connector on the end of this line and its associated rinse port are color-coded red on a CE-marked machine and purple on a non CE-Marked machine, and uniquely sized to prevent misconnection. During rinse, storage, or when the machine is operated for an acetate procedure, this line is connected to its rinse port.
23. Sample Port: A sample of the bicarbonate solution can be withdrawn from this port using a syringe. The conductivity should be checked before dialysis when the machine is operated for a bicarbonate procedure.
24. Bicarbonate Concentrate Line and Rinse Port: This concentrate line connects to the bicarbonate concentrate container when the machine is operated for a

bicarbonate procedure. The connector on the end of this line and its associated rinse port are color-coded blue on a CE-Marked machine and orange on a non CE-Marked machine, and uniquely sized to prevent misconnection. During rinse, storage, or when the machine is operated for an acetate procedure, this line is connected to its rinse port.

25. Chemical Port: During the disinfect cycle, the bicarbonate concentrate line is connected to this chemical port which is clear (translucent) on a CE-Marked machine. For non CE-Marked machines, this connector can be either green or translucent.
26. Locking Caster: The front casters swivel and lock. The rear casters are fixed.
27. Cuff Holder: The Centry BP cuff holder consists of velcro tape attached to a plexiglass piece that can be mounted on either side of the machine.
28. Centry BP Cuff: The Centry BP cuff is attached to the internal electronic module with a piece of tubing connected to a blood pressure monitor cuff connector at the rear of the machine. The tubing is nine feet long, allowing the cuff to be used on either the right or left side of the machine.
29. BiCart Holder: The BiCart holder is attached to the front panel of the machine. The arms of the holder will be open with a BiCart column inserted when performing BiCart dialysis. The arms of the holder should be closed when either acetate dialysis or bicarbonate jug dialysis is being performed.
30. BiCart Column: The BiCart column contains approximately 720 grams of sodium bicarbonate powder. After priming for BiCart dialysis, the machine will automatically proportion acid, water, and bicarbonate powder to produce approximately 200 liters of dialysis fluid for bicarbonate therapy.
31. Waste Handling Option (WHO): The WHO consists of a drain port, a rinse arm, and an angled housing, which maximizes ease of use. The drain port links to the priming connector on the COBE Cartridge set to dispose of the waste fluids produced during priming of the dialysis equipment.

8.4.4 OPERATOR CONTROL PANEL

The control panel for the machine consists of pushbuttons located next to the display screen. The buttons are grouped together by functions, screen selections, and a special option button (Fig. 18):

a. Functions Buttons (Identify with circles).
b. Screen Selection Buttons (Identify with squares).
c. Charts/bp Option Button (Identify with a Diamond.
d. Multiple Function Buttons (Identify with Triangles).

8.4.5 VIDEO DISPLAY SCREEN

Various screen displays assist the operator in setting up and monitoring dialysis. These screen displays can be grouped together under four categories:

1. **Mode Selection Screens:** Pressing the mode button displays the mode selection screens. This screen enables the operator to safely select several operating modes for the machine.

2. **Parameter Selection Screens:** The parameter selection screens display when the heparin, dialysate, or pressure/UFC screen buttons are pressed. These screens enable the operator to set the operating parameters for each dialysis procedure. The pressure/UFC screen also enables the operator to monitor the ultrafiltration data and the arterial and venous pressures during the procedure.
3. **Information Screens:** Information screens display when the status or alarm screen buttons are pressed. These screens give the operator the current status of the dialysis procedure or the current alarm conditions.
4. **Option Screens:** Pressing the options button displays the options that have been enabled. This screen lets the operator know which options are currently available on the machine.

8.4.6 BLOOD PUMP CONTROL PANEL

The flow rate display and controls related to the blood pump are located directly above the pump.

1. *Blood Pump Flow Rate Display:* The blood pump flow rate is shown in milliliters per minute. "888″ displays during the power supply test. "0″ displays when the blood pump is off (either because the operator or an alarm stopped it). The "0″ flashes when the blood pump is loading or unloading. During the venous phase of optional single needle dialysis (when the blood pump is stopped), the selected flow rate is displayed. "—" displays when the prime button has been pressed and the blood pump is ready to run in reverse. It also displays while the blood pump is running in reverse. The selected flow rate displays when the blood pump runs in the forward direction.
2. *Increase/Decrease Buttons:* The upward and downward pointing arrows are used to set the blood pump flow rate from 50 to 500 milliliters per minute (ml/min), in increments of 10 mL/min.

8.4.7 INSTALLATION

a. Environmental Requirements

Electrical: The machine operates satisfactorily from an electrical power source that delivers 90 to 132 volts AC, 48 to 62 Hz. It is rated at 12 amperes, 115 volts, 50/60 Hz. The high voltage machine operates satisfactorily from an electrical power source that delivers 180 to 264 volts AC, 48 to 62 Hz. It is rated at 6.25 amperes, 220/240 volts, 50/60 Hz. It is essential that the power receptacle is properly grounded and in good condition. Use of a potential equalization conductor is not applicable to this equipment.

Water Supply: For the operation of the unit, we need a minimum water pressure of 1.1 kg/cm^2 (15 psi) at a machine flow rate of 750 mL/min (approximately 12 gph). The cold water outlet must be adapted to mate with the ¾ inch female garden hose thread connector on the inlet water supply hose. Incoming water temperature must be between 1.7° C and 32.2° C (35° F and 90° F). To avoid precipitate buildup in the fluid pathway of the machine, water quality must meet the ANSI/AAMI RD-5–1992 approved American National Standard for Hemodialysis Systems. The maximum specified level for calcium and magnesium in the supply water is: 2 mg/L (0.1 mEq/L) of

calcium and 4 mg/L (0.3 mEq/L) of magnesium. The required water quality can be consistently achieved by treating the water with a deionizer or reverse osmosis system. Whenever using such devices, use only stainless steel or plastic fittings between the device and the unit. The water must be analyzed on a periodic basis to verify quality.

Drain: The machine requires a drain with the capacity of at least 750 mL/min (12 gallons per hour). Drain height cannot exceed 183 cm (6 feet).

Space: GAMBRO Renal Care Products recommends that the machine be located no more than 152 cm (5 feet) from utility connections. A minimum of 61 cm (2 feet) should be allowed for operator access on the three sides away from the patient.

Operational Setup:

1. Remove the plugs from the water supply and drain hoses. Check that the filter screen is in place in the water supply hose connector; then connect the hose to a treated water source.
2. Place the drain hose in the drain.
3. Verify that the dialysate hoses and concentrate lines are connected to the appropriate ports.
4. Check that the power switch on the front panel is off. Check the electrical receptacle to make sure that is properly grounded and good condition. Plug the power cord into the receptacle.
5. Turn the water on and check that water is not flowing through the machine into the drain.
6. Check the master controller printed circuit card (in the upper compartment of the machine) to verify that the calibration switch (SW2) is down.
7. Press the power switch on.
8. Press the fill softkey. When fluid is exiting the rain hose, press the continue softkey.
9. Place the dialysate hoses in a bucket of water and press both bypass port sensor switches.
10. When air separator low alarms occur, press the reset button. Continue until there is no more water being pulled into the dialysate hoses and no more air separator low alarms occur. Place the dialysate hoses on the bypass ports. Press the continue softkey.
11. Move the calibration switch (SW2), on the master controller printed circuit card, to the up position.
12. Replace the rear panel, the two side panels, and the top panel.
13. Replace the eight screw fasteners on the rear panel.
14. Remove the blood pump handcrank from the spares kit box, and hang the handcrank on the bracket on the back of the machine.
15. Before using the unit, disinfect it.

8.4.8 OPERATING INSTRUCTIONS FOR THE UNIT

a. Operating Instructions: Double Needle

Set Up Equipment

1. Check utilities: Power cord plugged in; Hose in drain; Water on; Dialysate hoses on bypass ports; and Power on or press setup softkey.
2. Set dialysate parameters (dialysate screen): Dialysate type; Dialysate temperature; Sodium level (Programmable Sodium option only: Verify on is highlighted on programmable sodium option screen #1 and that the sodium icon appears on the screen. Set sodium level 1 on programmable sodium option screen #2); and Bicarbonate level (if bicarbonate dialysate is selected).
3. Connect concentrate lines, and verify pH probe function.
4. Place the BiCart column in the BiCart holder.
5. Prime the BiCart column.
6. Initiate Autotest.
7. Test WHO for proper operation.

Set Up Disposables

1. Place dialyzer in holder.
2. Attach COBE Cartridge set: Open blood pump cover: Place COBE Cartridge pump segment in pump and COBE Cartridge in holder; Insert venous blood line into air bubble detector; Close blood pump cover; Insert venous blood line in venous line clamp and arterial blood line in arterial line holder; Connect venous and arterial dialyzer lines to dialyzer; Place COBE Cartridge saline, venous access, arterial access, and heparin lines in their clamps and clasp; Connect heparin-filled syringe to heparin line; and Place heparin syringe in holder.
3. Hang saline container: Clamp saline administration set; Connect saline administration set to saline container and hang; Connect end of saline administration set to venous blood line; and Insert the priming connector on the arterial blood line into the WHO drain port or over a collecting basin.
4. Verify conductivity and pH (if pH probe function was not verified when connecting concentrate lines).

Prime Disposables

1. Prime dialyzer. (Instructions apply to hollow fiber dialyzers only): Press prime button.
2. Set heparin parameters (heparin screen): Unclamp heparin line: Prime heparin line: Clamp heparin line: and Set heparin infuse rate and infuse stop time.
3. Unclamp saline administration set and venous blood line: Start blood pump: Raise fluid level in venous chamber, if necessary: Clamp and release saline administration line or venous patient line to eliminate air in the COBE Cartridge.
4. Raise fluid level in arterial chamber: Tap dialyzer; Unclamp COBE Cartridge saline or arterial access line; Fill arterial chamber to bottom of the diaphragm; Clamp COBE Cartridge saline line or arterial access line.
5. Attach dialysate hoses to dialyzer.
6. Discontinue priming.
7. Recirculate saline: Connect patient ends of venous and arterial blood lines; Select recirculate; Unclamp arterial and venous blood lines; Recirculate with ul-

trafiltration rate greater than 0 kg/hr (if recirculating with blood pump running in reverse); Start blood pump; and Recirculate per unit protocol.

8. Initiate automated alarms tests.
9. Perform venous pressure high alarm test: Access pressure/UFC screen; Open pressure alarm limits by increasing or decreasing blood pump speed by 10 mL/min; Clamp the venous blood line below the COBE Cartridge. Observe venous pressure increase until venous/pressure high alarm occurs and blood pump stops; and Press the reset button, then press Resume to continue.

Activate and setup CentryNet Option

1. Press the set patient ID softkey on the ready screen.
2. Verify station ID to be sure that posted station ID matches assigned station id displayed on the screen.
3. Enter patient ID.
4. Press start treatment softkey.

Activate the charts/BP option

1. Apply blood pressure cuff.
2. Press charts/bp button.
3. Take predialysis blood pressure readings.
4. Press settings softkey and set automatic intervals for data collection and liters to process (if desired) for the current treatment.
5. Press charts/bp button.
6. Press BP limits softkey and select blood pressure alarm limits from the BP limits screen.

Initiate Dialysis

1. Heparinize patient.
2. Set ultrafiltration parameters (pressure/UFC screen): Procedure time; and Target weight loss.
3. Set optional programmable sodium parameters (programmable sodium option screen #2); Sodium level 2 and level 3; and Sodium level times 1 and 2.
4. Fill circuit with fresh saline: Stop blood pump: Clamp venous and arterial blood lines; Disconnect the arterial blood line from the priming connector, leaving the priming connector on the venous blood line; Place the arterial blood line over basin, being careful to not contaminate the line; With blood pump off, unclamp saline administration set, COBE Cartridge saline line and arterial blood line; Allow 60 mL of saline to run out of saline bag; Clamp arterial blood line; Connect arterial blood line to patient's arterial access line (Leave lines clamped); Start blood pump; Unclamp venous blood line; Flush remaining circuit; and Stop blood pump and clamp venous blood line.
5. Connect patient: Verify that the requirements for performing the autotest have been met; If autotest was not performed since the previous treatment, verify that the previous patient's weight removal was within normally expected limits. If not, perform the autotest before connecting the patient; Verify no alarms (except not in dialyze mode alarm); Unclamp arterial blood line and patient's

arterial access line; Start blood pump; Unclamp venous blood line; When blood enters venous chamber, clamp venous blood line and stop blood pump; Connect venous blood line to patient's venous access line; Unclamp venous blood line and patient's venous access line; and Start blood pump and set flow rate.

6. Dialyze patient: Press dialyze softkey; Unclamp heparin line; Set heparin bolus, if bolus is to be given and press start bolus softkey on the heparin screen; Wait 5 min, access dialysate screen, and set maximum TMP based on TMP displayed on status screen; and Press pressure/UFC button to access pressure/UFC screen.
7. Transfer Charts data to paper treatment form (If using the CentryNet option, ignore these instructions); Press charts/bp button to access the charts/BP screens; Press charts softkey to access charts screens; and Transfer machine and patient data from charts screens as needed.

Discontinue Dialysis

1. Rinseback blood to patient; Stop blood pump; Clamp venous blood line; Clamp arterial blood line, patient's arterial access line, and heparin line; Clamp saline administration set; Disconnect saline administration set from COBE Cartridge saline line; Disconnect arterial blood line from patient's arterial access line; Connect arterial blood line to saline administration set; Unclamp and flush patient's arterial access line; Clamp patient's arterial access line; Unclamp arterial blood line, saline administration set, and venous blood line; Start blood pump and set flow rate; Clear dialyzer and blood lines of red blood cells; Stop blood pump and clamp venous blood line; Clamp patient's venous access line; and Disconnect venous blood line from patient's venous access line.
2. Complete recording machine and patient data from charts/BP screens onto paper treatment form (If using CentryNet option, ignore these instructions): Press charts/bp button; Take postdialysis blood pressure readings; Remove blood pressure cuff from patient; Press charts softkey to access recorded machine and patient data; Transfer data to paper treatment form as needed 3. Remove disposables; Clamp saline administration set; Disconnect saline administration set from arterial blood line; Connect arterial blood line to arterial access line; Connect venous blood line to venous access line; Remove heparin syringe from holder; Disconnect heparin syringe from heparin line; Connect heparin line to COBE Cartridge saline line; Unclamp COBE Cartridge saline, venous access, arterial access, and heparin lines. Ensure both the arterial and venous blood lines are clamped; Press the MODE softkey and the rinseback softkey; Open blood pump cover; Remove arterial blood line from arterial line holder; Remove venous blood line from venous line clamp and air bubble detector; Remove COBE Cartridge from holder and COBE Cartridge pump segment from pump; Remove dialyzer from holder; Disconnect dialysate hoses from dialyzer; Place dialysate hoses on bypass ports.-Close blood pump cover; Press the mode softkey and the setup softkey; If blood has gone down the WHO drain port, the WHO bleach procedure must be performed prior to

setting up for the next patrient; Remove the BiCart column and discard; and Clean the BiCart holder arms and close them securely.

3. Complete recording machine and patient data from charts/BP screens: Press charts/bp button; Take postdialysis blood pressure readings; Remove blood pressure cuff from patient; Press the options button and access the CentryNet screens; and Press end treatment softkey to conclude collecting data for the current patient.

Clean Machine

1. If performing BiCart dialysis, verify the BiCart holder arms are closed.
2. Place the WHO rinse arm in the WHO drain port: Initiate clean cycle.
3. Connect acetate concentrate line to yellow chemical port.
4. When cycle completes, connect acetate concentrate line to rinse port.
5. Press "press when complete" softkey.

Perform Acid Rinse

1. If performing BiCart dialysis, verify the BiCart holder arms are closed.
2. Initiate acid rinse cycle.
3. Connect bicarbonate concentrate line to container of vinegar.
4. After acid intake, return concentrate connector to rinse port.
5. Press "press when complete" softkey.
6. If a toxic chemical is used, rinse machine again.
7. Return to setup screen or turn power off.

b. Operating Instructions: Single Needle

Set Up Equipment

1. Check utilities: Power cord plugged in: Hose in drain: Water on: Dialysate hoses on bypass ports: and Power on or press setup softkey.
2. Set dialysate parameters (Dialysate screen): Dialysate type; Dialysate temperature; Sodium level (Programmable sodium option only – Verify **on** is highlighted on programmable sodium option screen #1 and that the sodium icon appears on the screen. Set sodium level 1 on programmable sodium option screen #2); and Bicarbonate level (if bicarbonate dialysate is selected).
3. Connect concentrate lines and verify pH probe function.
4. Place the BiCart column in the BiCart holder.
5. Prime the BiCart column.
6. Initiate Autotest.
7. Test WHO for proper operation.

Set Up Disposables

1. Place dialyzer in holder.
2. Attach COBE Cartridge set: Open blood pump cover; Place COBE Cartridge pump segment in pump and COBE Cartridge in holder; Insert venous blood line into air bubble detector; Close blood pump cover; Insert venous blood line in venous line clamp and arterial blood line in arterial line clamp; Insert predialyzer and postdialyzer pumping chambers in chamber clips and close

slide clamps on monitoring lines; Connect venous and arterial dialyzer lines to dialyzer; Place COBE Cartridge saline, venous access, arterial access, and heparin lines in their clamps and clasp; Connect heparin-filled syringe to heparin line; and Place heparin syringe in holder.

3. Hang saline container: Clamp saline administration set; Connect saline administration set to saline container and hang; Connect end of saline administration set to venous blood line; Insert the priming connector on the arterial blood line into the WHO drain port or over a collecting basin; Verify conductivity and pH (if pH probe function was not verified when connecting concentrate lines).

Prime Disposables

1. Prime dialyzer. (Only apply to hollow fiber dialyzers): Press prime button.
2. Set heparin parameters (heparin screen): Unclamp heparin line; Prime heparin line; Clamp heparin line; and Set heparin infuse rate and infuse stop time.
3. Unclamp saline administration set and venous blood line: Start blood pump; Clamp venous blood line between air bubble detector and venous chamber for 15 sec; Do not adjust fluid levels in pumping chambers unless fluid rises above the level that is achieved when the blood pump is running forward; Raise fluid level in venous chamber, if necessary; and Clamp and release saline administration line or venous blood line to eliminate air in the COBE Cartridge.
4. Raise fluid level in arterial chamber; Tap dialyzer: Unclamp COBE Cartridge saline line or arterial access line; Fill arterial chamber to the bottom of the diaphragm; Clamp COBE Cartridge saline line or arterial access line.
5. Attach dialysate hoses to dialyzer.
6. Discontinue priming.
7. With blood pump off, access pressure/UFC screen and allow venous pressure to stabilize between 0 and +10 mmHg.
8. Clamp venous blood line.
9. Recirculate saline: Connect patient ends of venous and arterial blood lines; Select recirculate; Unclamp arterial and venous blood lines; Recirculate with ultrafiltration rate greater than 0 kg/hr (if recirculating with blood pump running in reverse); Start blood pump; and Recirculate per unit protocol.
10. Initiate automated alarms test.
11. Perform venous pressure high alarm test: Access pressure/UFC screen; Open pressure alarm limits by increasing or decreasing blood pump speed by 10 mL/min; Clamp the venous blood line below the COBE Cartridge, and observe venous pressure increase until venous/pressure high alarm occurs and blood pump stops; Press the reset button, then press Resume to continue.

Initiate Dialysis

1. Heparinize patient.
2. Set ultrafiltration parameters (pressure/UFC screen): Procedure time; and Target weight loss.

3. Set **single needle parameters (SN option screen)**: Verify on is highlighted on SN option screen and single needle icon appears on the screen: Set venous high pressure and low pressure trip points.
4. Set optional programmable sodium parameters (programmable sodium option screen #2): Sodium level 2 and level 3; and Sodium level times 1 and 2.
5. Fill circuit with fresh saline: Stop blood pump; Clamp venous and arterial blood lines; Disconnect the arterial blood line from the priming connector, leaving the priming connector on the venous blood line; Place the arterial blood line over basin, being careful to not contaminate the line; With blood pump off, unclamp saline administration set, COBE Cartridge saline line and arterial blood line; Allow 60 mL of saline to run out of saline bag; Clamp arterial blood line; Connect arterial blood line to patient's arterial access line. (Leave lines clamped); Start blood pump; Unclamp venous blood line; Flush remaining circuit; and Stop blood pump and clamp venous blood line.
6. Connect patient: Verify that the requirements for performing the Autotest have been met; If Autotest was not performed since the previous treatment, verify that the previous patient's weight removal was within normally expected limits (If not, perform the Autotest before connecting the patient); Verify no alarms (except not in dialyze mode alarm); Unclamp arterial blood line and patient's arterial access line; Start blood pump; Unclamp venous blood line; When blood enters venous chamber, clamp venous blood line and stop blood pump; Connect venous blood line to patient's venous access line; Unclamp venous blood line and patient's venous access line; and Start blood pump and set flow rate.
7. Dialyze patient: Press dialyze softkey; Unclamp heparin line; Wait 5 min, access dialysate screen, and set maximum TMP based on TMP displayed on status screen; Set heparin bolus, if bolus is to be given and Press start bolus softkey on the heparin screen; and Press pressure/UFC button to access pressure/UFC screen.
8. Transfer Charts data to paper treatment form: Press charts/bp button to access the charts/BP screens; Press charts softkey to access charts screens; Transfer machine and patient data from charts screens as needed.

Discontinue Dialysis

1. Rinseback blood to patient: Stop blood pump; Clamp venous blood line; Clamp arterial blood line, patient's arterial access line, and heparin line; Clamp saline administration set; Disconnect saline administration set from COBE Cartridge saline line; Disconnect arterial blood line from patient's arterial access line; Connect arterial blood line to saline administration set; Unclamp and flush patient's arterial access line; Clamp patient's arterial line; Unclamp arterial blood line, saline administration set, and venous blood line; Start blood pump and set flow rate; Clear dialyzer and blood lines of red blood cells; Stop blood pump and clamp venous blood line; Clamp patient's venous access line; and Disconnect venous blood line from patient's venous access line.

2. Complete recording machine and patient data from charts/BP screens onto paper treatment form: Press charts/bp button; Take postdialysis blood pressure readings; Remove blood pressure cuff from patient; Press charts softkey to access recorded machine and patient data; and Transfer data to paper treatment form as needed.
3. Remove disposables: Clamp saline administration set; Disconnect saline administration set from arterial blood line; Connect arterial blood line on arterial access line; Connect venous blood line to venous access line; Remove heparin syringe from holder; Disconnect heparin syringe from heparin line; Connect heparin line to COBE Cartridge saline line; Unclamp COBE Cartridge saline, venous access, arterial access, and heparin lines (Ensure both the arterial and venous blood lines are clamped); Press the MODE softkey and the rinseback softkey; Open blood pump cover; Remove arterial blood line from arterial line holder; Remove venous blood line from venous line clamp and air bubble detector; Remove pumping chambers from their clips; Remove COBE Cartridge set from holder and COBE Cartridge pump segment from pump; Remove dialyzer from holder; Disconnect dialysate hoses from dialyzer; Place dialysate hoses on bypass ports; Close blood pump cover; Press the mode softkey and setup softkey; If blood has gone down the WHO drain port, the WHO bleach procedure must be performed prior to setting up for the next patient; Remove the BiCart column and discard; and Clean the BiCart holder arms and close them securely.
4. Complete recording machine and patient data from charts/BP screens; Press charts/bp button; Take postdialysis blood pressure readings; Remove blood pressure cuff from patient; Press the options button and access the CentryNet screens; and Press end treatment softkey to conclude collecting data for the current patient.

Clean Machine

1. If performing BiCart dialysis, verify that the BiCart holder arms are closed.
2. Place the WHO rinse arm in the WHO drain port.
3. Initiate clean cycle.
4. Connect acetate concentrate line to yellow chemical port.
5. When cycle completes, connect acetate concentrate line to rinse port.
6. Press “Press when complete” softkey.

Perform acid rinse

1. If performing BiCart dialysis, verify the BiCart holder arms are closed; then initiate acid rinse cycle.
2. Connect concentrate line to container of vinegar.
3. After acid intake, return concentrate connector to rinse port.
4. Press “Press when complete” softkey.
5. If a toxic chemical is used, rinse machine again.
6. Return to setup screen or turn power off.

8.4.9 PREVENTIVE MAINTENANCE

a. Instructions For the ACDR Cycle

During operation of the ACDR mode, the dialysate hoses must be connected to the by-pass ports. Ensure that the blood pump cover is closed. If machine power is interrupted during an ACDR cycle, a forced rinse occurs, lasting approximately 18.5 min. If the bicarbonate sample port leaks during an ACDR cycle, it may be caused by:

1. A high flow rate: (A qualified service technician can adjust this by recalibrating the flow rate for the cycle).
2. Precipitate buildup, which causes a large leak (can be remedied by performing either a nitric or citric acid rinse cycle).
3. A faulty sample port, which causes a small leak (A qualified service technician can eliminate the leak by installing a new sample port).

b. After Each Dialysis

Exterior Cleaning: With mild soap in water. Procedure is as follows:

1. Wipe dried blood and other organic material off the machine, using a mild soap and water solutions.
2. Rinse the dialysate hose connectors in warm water that meets AAMI standards for the hemodialysis water to remove salt deposits.
3. If performing BiCart dialysis, clean the exterior of the BiCart holder and the lower arms joint.

Exterior Disinfection: With 5.25–6% Sodium hypochlorite (Commercial Household Bleach). Procedure is as follows:

1. Use a cloth dampened with 0.5% sodium hypochlorite solution to wipe down the cabinet and the cabinet and the blood pump. Commercial household bleach (5.25–6% sodium hypochlorite) when diluted 1 part bleach with 9 parts water yields approximately 0.5% sodium hypochlorite.
2. To wipe down the blood pump, open the blood pump cover; then press the latching pin on the top of the clear, plastic cover door and swing the door open. Do not spray bleach into the pump. Instead, apply with a dampened rag. After cleaning the pump, swing the cover door closed until it latches in place; then close the blood pump cover.
3. Allow the unit air to dry.

c. WHO System Cleaning:

1. If blood goes down the drain port, perform the WHO bleach procedure as follows (Non-sterile components can be used when bleaching the WHO system):
   - Using a syringe with the priming connector as an adapter, inject 15cc of undiluted bleach (5.25–6% sodium hypochlorite) into the WHO system.
   - Remove the syringe and priming connector. Reposition the WHO rinse arm in the drain port. Failure to reposition the rinse arm in the drain port may result in incomplete rinseout of the bleach.
   - Allow the machine to rinse for 5 min prior to setting up for the next patient.

2. In order for rinsing of the WHO system take place (after use, during the rinse portion of the bleach procedure, and during any ACDR procedure) the rinse arm must be positioned in the drain port.

8.4.9.1 DAILY RINSING

When bicarbonate dialysis is performed, daily acid rinsing with vinegar acid concentrate is necessary to control precipitate buildup in the fluid pathway. Acid rinsing may not be required when using Actril daily as a flow path disinfectant, but periodic acid rinsing may still be necessary if precipitation occurs. The following 13-minutes procedure can be performed at any time during the day when patient is not connected to the machine.

1. Press the mode button; then press ACDR softkey. Select ACID RINSE.
2. Connect a container of at least 400 mL of white distiled vinegar (preferred for higher acidic content) or acid concentrate to the bicarbonate concentrate line.
3. After 6.5-minute acid fill phase, return the concentrate connector to its rinse port and press the PRESS WHEN COMPLETE softkey. The machine then automatically rinses out the acid in 6.5 min.

8.4.9.2 DAILY CLEANING

Using 5.25–6% Sodium hypochlorite, use the following procedure:

1. Verify that the cleaning chemical container (color-coded yellow) connected at the back of the machine contains at least 250 mL of sodium hypochlorite.
2. Press the mode button, then the ACDR softkey, select CLEAN.
3. Insert the acetate concentrate line in the yellow chemical port and press the PRESS WHEN COMPLETE softkey.
4. When the ACDR CYCLE COMPLETE alarm occurs, place the acetate concentrate line in its rinse port and the PRESS WHEN COMPLETE softkey.

8.4.9.3 DAILY DISINFECTING (ACTRIL)

The recommended disinfectant dilution and dwell time (below) are set when the machine is calibrated during installation. If a change in disinfectant or dwell time is required, consult your service technician listed under “service information” to reset this parameter. Routine or maintenance levels of disinfection may be inadequate when incoming water levels contains microorganism levels higher than AAMI guidelines, or when yeast, molds, or other fungi accumulate on the filter screens. When these conditions exist, contact your service technician or service technician listed under “service information” for higher level disinfection recommendations.

8.4.9.4 WEEKLY RINSING USING 6% OR 1N NITRIC ACID

Weekly nitric acid rinsing is necessary to remove the buildup of precipitate in the fluid pathway. Nitric acid rinsing may not be required when using Actril daily as a flowpath disinfectant, but periodic rinsing with nitric acid may still be necessary if precipitation occurs. The 13 min procedure (not including additional rinsing) should be performed prior to disinfecting the machine in order to use the automatic prerinse in the disinfect cycle. Otherwise, an 18.5 min ACDR rinse cycle should be performed after nitric acid rinsing in order to ensure complete rinseout of this toxic chemical.

1. Prepare 500 mL of 6% nitric acid (approximately 1.0 Normal) in a plastic or glass container, and connect to the bicarbonate concentrate line. The unit automatically dilutes the acid to 0.6% (approximately 0.1 N).
2. Press the mode button; then press the ACDR softkey. Select acid rinse.
3. After the 6.5 min acid fill phase, return the concentrate connector to its rinse port and press the press when complete softkey.

8.4.9.5 WEEKLY RINSING USING CITRIC ACID

Citric acid is an acceptable alternative to nitric acid for use in the weekly acid rinsing procedure on COBE dialysis machines performing bicarbonate therapy. Citric acid is as effective as nitric acid, but it is easier to handle. No special preparation is necessary in order to switch from nitric acid to citric acid rinsing. Citric acid rinsing may not be required when using Actril daily as a flowpath disinfectant, but periodic rinsing with citric or nitric acid may still be necessary if precipitation occurs. The 13 min procedure (not including additional rinsing) should be performed prior to disinfecting the machine.

1. Prepare a 20% solution of citric acid by dissolving 100 grams of citric acid in 500 mL of AAMI standard water.
2. Place the 20% solution in a plastic or glass container. Connect the citric acid solution to the bicarbonate concentrate line.
3. Press the mode button; then press the ACDR softkey. Select acid rinse and press the “press when complete” softkey.
4. After the 6.5 min acid fill phase, return the concentrate connector to its rinse port and press the “press when complete” softkey.

8.4.9.6 WEEKLY CLEANING

1. Disconnect the dialysate hoses from the bypass ports.Place the connectors in a 0.1% bleach solution (1 part of 5.25% sodium hypochlorite bleach to 49 parts water) for 1 hr. Before the connectors are removed from the bleach solution, move the flange several times to ensure that the inside surfaces of the connector are cleaned.
2. Thoroughly rinse the connectors in water that meets the AAMI Standard for water use in hemodialysis.
3. Reconnect the dialysate hoses to the bypass ports.

8.4.9.7 WEEKLY DISINFECTING (FORMALDEHYDE ACTRIL)

The recommended disinfectant dilutions and dwell times (below) are set when the machine is calibrated during installation. Routine or maintenance levels of disinfection may be inadequate when incoming water levels contain microorganism levels higher than AAMI guidelines, or when yeast, molds, or other fungi accumulate on the filter screens.

8.4.10 BLOOD PRESSURE MONITOR DAILY CARE

Visual Inspection: Inspect the tube, which connects the Centry BP cuff to the unit for wear or damage. If the tube appears damaged in any way, replace it as soon as possible.

Cleaning:

1. If the cuff has become soiled, clean the exterior surface of the cuff with a cloth or sponge dampened in a solution of warm water and a mild detergent.
2. Wring excess moisture from the fabric to speed the drying process.

8.4.11 MACHINE LAUNDERING

The blood pressure cuff may be machine laundered, if desired.

1. Insert fingers in the opening on the lower edge of the cuff, and fold or roll up the bladder inside the cuff.
2. Remove bladder through the opening.
3. Put the Velcro or hook and loop surfaces together.
4. Wash on delicate cycle only.
5. Reinstall the air bladder.

8.5 CONCLUSIONS

Our kidneys remove waste and excess fluid, filter the blood, control the production of red blood cells, and release hormones that help regulate blood pressure, among other functions. Sometimes the kidneys fail due to diseases and disorders. When this occurs the patient has several options, such as: Start a dialysis treatment, choosing between peritoneal dialysis and hemodialysis, or have a kidney transplant, however, not every patient is eligible for a transplant. Before the dialysis devices were available, total kidney failure meant death. Today, people with kidney failure can live because of treatments like dialysis and kidney transplant.

8.6 SUMMARY

The function of the kidney system is to eliminate toxic wastes produced by other bodily functions and to eliminate extra fluids. When complete renal failure occurs, the use of an artificial kidney is required. An artificial kidney is a machine that provides a means for removing undesirable substances from the blood and adding needed components to it. This is done using the principle of dialysis. There are two types of dialysis treatment: peritoneal dialysis and hemodialysis. The peritoneal dialysis is done at home and hemodialysis is done at the hospital or a dialysis unit. Dialysis treatment can have its side effects, although this can be avoided with a good hygiene.

KEYWORDS

- **Arterio venous fistula**
- **Arterio venous graft**
- **Artificial kidney**
- **CAPD**
- **Catheter**
- **Continuous ambulatory peritoneal dialysis**
- **Convection**
- **Dialysate**

- **Dialysis**
- **Diffusion**
- **Hemodialysis**
- **Hemofiltration**
- **Hypertension**
- **Kidney**
- **Mesothelium**
- **Nephrons**
- **Osmosis**
- **Peritoneal dialysis**
- **Peritoneal membrane**
- **Peritonitis**
- **Ultrafiltration**
- **Vascular access**

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APPENDIX 1: NUMERICAL EXERCISES

1. Blood is pumped from the artificial kidney at a total flow rate of 0.003 m/s^2, through the nozzle of 15 mm in diameter. Calculate the blood velocity using continuity equation.
   $V = Q/A = (0.003)/((\pi/4)(0.15)^2) = 0.1698$ m/s
2. How much normal force is exerted on the kidney with a surface area 4.1 in^2 and for a flow pressure of 103 psi?
   $F = (P)(A) = (103 \text{ psi})(4.1 \text{ in}^2) = 422.3$ lb
3. If the specific gravity of fluid used by an artificial kidney is 1.22, determine the density of the fluid.
   $\rho = 1.22 \times 1000 \text{ kg/m}^3 = 1{,}220 \text{ kg/m}^3$
4. Calculate the creatinine countercurrent clearance of a Dow Model-5 to be operated at Q_B = 180 mL/min and Q_D = 600 mL/min. K_DO = 156 mL/min. For Model Dow 5 counter – current, use: creatinine Q_B = 200 mL/min, Q_D = 500 mL/min.

$$h_o A = 333 \ln \left[\frac{1 - \frac{156}{500}}{1 - \frac{156}{200}} \right] = 380 \text{ ml/min}$$

5. For urea (molecular weight, MW = 60), vitamin B_{12} (MW = 1355), and albumin (MW = 66000), determine the resistances offered by the blood, mem-

brane, and dialysate for the following conditions for hollow-fiber membranes. Following data is known:

<table>
<tr><td colspan="3">Urea diffusion coefficient at 37° C = 1.81 × 10–5 $cm^2\ s^{-1}$
D_m/D_{ij} for urea = 0.16
Vitamin B_{12} diffusion coefficient at 37° C = 4.5 × 10–6 $cm^2\ s^{-1}$
D_m/D_{ij} for vitamin B_{12} = 0.05
Albumin diffusion coefficient at 37° C = 6.34 × 10–7 $cm^2\ s^{-1}$
D_m/D_{ij} for albumin = 2 × 10^{-5}</td><td colspan="2">Dialysate mass transfer coefficient, cm min^{-1} (k_D) = 126.103 $(D_{ij})^{2/3}$
Surface area of exchanger = 1.5 m^2
Shear rate = 250 s^{-1}
Membrane thickness = 20 μm
Inner diameter of hollow fiber d = 180 μm</td></tr>
<tr><td>For the blood phase, the mass transfer resistance is:
$R_B = \frac{1}{k_B} = \frac{d}{4.30\left(0.53D_{ij} + 5.292\times10^{-9}\gamma_w\right)}$</td><td>The membrane resistance is:
$R_m = \frac{L_m}{D_m}$</td><td>The dialysate resistance is:
$R_D = \frac{1}{126.103\left(D_{ij}\right)^{2/3}}$</td></tr>
</table>

The results are summarized as below:

Molecule	R_B	R_m	R_D	RO	R_m/RO
Urea	6.39	11.52	11.5	29.4	0.39
Vitamin B_{12}	18.8	148	29.1	196	0.76
Albumin	42	2.63 × 10^6	108	2,630,150	0.99

Comments: The absolute resistance increases with increasing size of the molecule. The membrane is most sensitive to the molecular size and becomes a greater fraction of the total mass transport resistance as the size increases.

APPENDIX 2: INTERVIEW WITH A NURSE

On June 9 of 2010, my students visited Mayaguez Medical Center in Puerto Rico. They had an opportunity to talk and spent time with Registred Nurse of the Dialysis Unit. She gave them a tour of the dialysis unit, the machine room and explained the dialysis device and its operation. She also provided information on different treatments in the dialysis process. The interview is summarized as below:

1. What is your name and what is your job in this dialysis unit?
   My name is Nurse Lucre and I am incharge of treatments to dialysis patients.
2. When is a dialysis treatment needed?
   A dialysis treatment is needed when our kidneys fail to do their function and we have to artificially filtrate the blood, which is dialysis treatment.
3. How often do patients come for treatment?
   Patients come for treatment three times a week. It could be Monday, Wednesday and Friday, or Tuesday, Thursday and Saturday. We have three different sessions: in the morning, in the afternoon, and in the evening.
4. How long does each dialysis treatment take?

It depends on the kind of treatment. If the patient is using peritoneal dialysis, the treatment last from 8 to 10 hours. If it is a hemodialysis treatment it last 3 to 4 hours.

5. Can you tell us about the dialysis machine?
   I can give you a booklet about the machine and its uses. But person that can really tell you about its functions and maintenance is the technician, and he is not here today.

CHAPTER 9

BIOMECHANICS OF ARTHRITIS AND HUMAN BODY PAIN[1,2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Waleska Echevaria, Damian Guzman and Yanaira Ocasio) for the course on Fluid Mechanics, INGE 4015. Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com> or visit at: http://www.ece.uprm.edu/~m_goyal/home.htm. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2]The numbers in parentheses refer to cited references in the bibliography.

9.1 INTRODUCTION

Arthritis is a leading cause of disability in the United States, affecting about one in every six Americans. It is one of the two most common forms: osteoarthritis or rheumatoid arthritis. These two forms of arthritis are part of a group of more than 100 rheumatic disorders. Arthritis, regardless of the cause, typically makes joints painful, stiff, and swollen. In order to present an initial idea of how arthritis affects the joints, Figs. 1 and 2 indicate the effects of arthritis in an arthritic hip joint. In the arthritic hip joint, it is possible to see the damaged cartilage in the ball of the femur and the area of the joint in the pelvis bone.

This chapter discusses causes, symptoms, statistical data, treatment, types of arthritis, the importance of the synovial fluid and research advances in biomechanics of the arthritis and human body pain. This information may help the patient to take decisions about the best options for the treatment of arthritis.

9.2 CAUSES OF ARTHRITIS

- Age – The older we are, the more likely we are to develop osteoarthritis.
- Sex – Women are more likely to develop osteoarthritis than men.
- Injury – Trauma causing injury to the cartilage may lead to arthritis. However, athletics or exercise without injury may help people with arthritis.
- Obesity – More weight across the joint leads to more arthritis. The overweight paerson has two to three times higher chances of developing arthritis compared to persons with normal body weight.
- Genetics – Only a very small percentage of people with osteoarthritis have a genetic link. However, even with a genetic link, medical treatment can provide tremendous relief of pain.
- Joint instability.
- Altered biochemistry of fluids around the joints.
- Hormonal factors.
- Environmental factors.
- Psychological factors.
- **Stress** disrupts the hormonal balance. Stress- induced cortisone deficiency can be a factor in some forms of arthritis. When stress occurs, body systems release adrenalin and cortisone, a process that weakens the immune system. As a result, bacteria and other detrimental organisms such as Candida albicans spread throughout the body.
- Arthritis And dental amalgams – Arthritic symptoms are often found to be associated with mercury dental amalgams. It has been found that once the amalgams are removed, the symptoms of arthritis usually disappear (36).

9.3 FACTS AND STATISTICS

Arthritis and chronic joint symptoms affect more than 70 million Americans, or about one of every three adults, making it one of the most prevalent diseases in the United States. Figure 3 and Table 1 show the percentage of adults aged 18 years or older with

arthritis or chronic joint symptoms, by State. As the population ages, this number can increase dramatically (31).

- Arthritis is the leading cause of disability among U.S. adults. It limits everyday activities of more than 7 million Americans. Figure 4 shows the leading causes of disability among U.S. adults.
- By 2020, an estimated 12 million Americans will be limited in daily activities because of arthritis. Figure 5 shows the projected region distribution.
- Arthritis is not just a disease for elderly persons: nearly two-thirds of people with arthritis are younger than 65 years.
- Each year, arthritis results in 44 million outpatient visits, 750,000 hospitalizations; with estimated medical care cost of more than $22 billion, and estimated total costs (medical care and decreased productivity) of $82 billion.

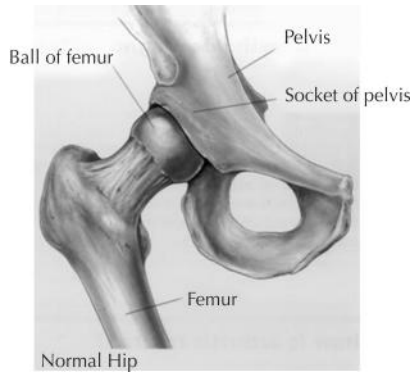

FIGURE 1 Normal Hip (11).

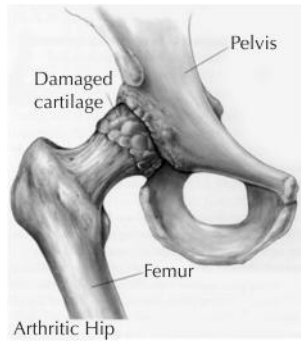

FIGURE 2 Arthritic Hip (11).

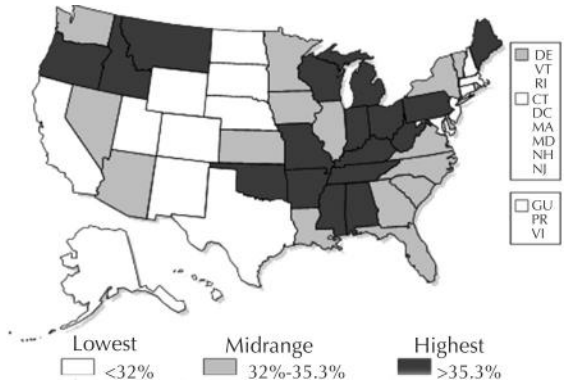

FIGURE 3 Percentage of adults (18 years or Older) with arthritis or chronic joint symptoms in U.S.A., (United States, Behavioral Risk Factor Surveillance System, 2003).

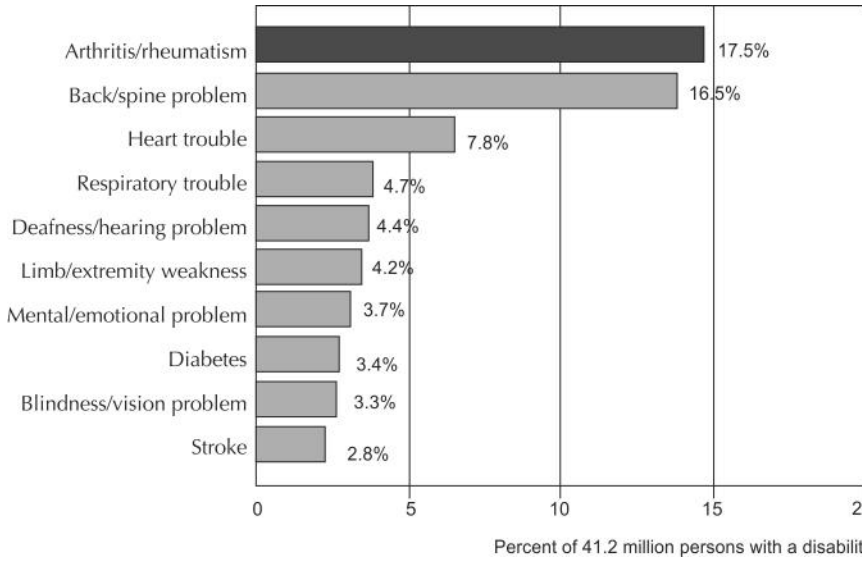

FIGURE 4 Leading causes of disability among adults in U.S.A. (31).

9.4 TYPES OF ARTHRITIS

9.4.1 INFLAMMATORY ARTHRITIS

"Arthritis" strictly means inflammation of the joints, but the term is used generally for almost all joint problems. Inflammatory arthritis means the diseases of joints, where the immune system is causing inflammation in the joint. The characteristic symptoms of inflammatory arthritis are pain and swelling of one or more joints that can be warmer than the adjoining areas. Stiffness of the joints on getting up in the morning, or after sitting still for a long time is very common and is sometimes the first symptom. The symptoms may begin after a minor illness such a sore throat or a cold, or may even be associated with a period of emotional stress such as bereavement. However,

there is no identifiable cause. Often similar symptoms will get better by itself after a few days, with bed rest or intake of simple painkillers, such as paracetamol (US: acetaminophen) (13).

9.4.2 AUTOIMMUNE DISEASES

The "autoimmune disease" refers to a varied group of more than 80 serious, chronic illnesses that involve almost every human organ system. In all of these diseases, the underlying problem is similar: Our immune system becomes misdirected, attacking the very organs it was designed to protect. About 75% of autoimmune diseases occur in women, most frequently during the childbearing years. Autoimmune diseases can affect connective tissue (This is the tissue which binds together various tissues and organs). It can also affect the nerves, muscles, endocrine system, and gastrointestinal system. Common examples of autoimmune diseases are Lupus, rheumatoid arthritis, and systemic sclerosis affecting the connective tissue; multiple sclerosis, myasthenia gravis, and Gullian-Barre syndromes are neuromuscular diseases. On the other hand, Hashimoto's thyroiditis, Graves' disease, and insulin-dependent/juvenile diabetes (type 1) are related to the endocrine system. Finally, inflammatory bowel disease is an autoimmune disease, which attacks the gastrointestinal system. Autoimmune diseases unfortunately are among the most poorly understood of any category of illness. It is thought that hormones play a role in inducing autoimmune diseases: some cases suddenly improve during pregnancy, some flareups occur after delivery, while others will get worse during pregnancy, or flare up after menopause.

TABLE 1 Percentage of adults aged 18 years or older with arthritis or chronic joint symptoms in the U.S.A. (31).

Lowest < 32.9%	**Midrange 32–35.3%**	**Highest > 35.3%**
Alaska California Colorado ConnecticutDistrict of Columbia Hawaii Maryland Massachusetts Nebraska New Hampshire New Jersey New Mexico North Dakota South Dakota Texas Utah Wyoming	Arizona Delaware Florida Georgia Illinois Iowa Kansas Louisiana Minnesota Nevada New York North Carolina Rhode Island South Carolina Vermont Virginia Washington	Alabama Arkansas Idaho Indiana Kentucky Maine Michigan Mississippi Missouri Montana Ohio Oklahoma Oregon Pennsylvania Tennessee West Virginia Wisconsin
Guam Puerto Rico U.S. Virgin Islands		

Autoimmune diseases seem to also have a hereditary component, but mysteriously, they can cluster in families as different illnesses. For example, a mother may have lupus erythematosus; her daughter, diabetes; her grandmother, rheumatoid arthritis. Research advances have contributed to identify the genetic, hormonal and environmental risk factors that enhance these diseases. The diagnosis of an autoimmune disease is based on the symptoms, findings from a physical examination, and results from laboratory tests. Autoimmune diseases are not easy to diagnose, especially in the early

stages of the disease. In some cases a specific diagnosis cannot be made; the patient must continue to follow up on the disease with frequent consultations with a physician. Although autoimmune diseases are chronic, the course they take is unpredictable. Patients should be monitored closely by the physician so environmental factors or triggers can be avoided (14).

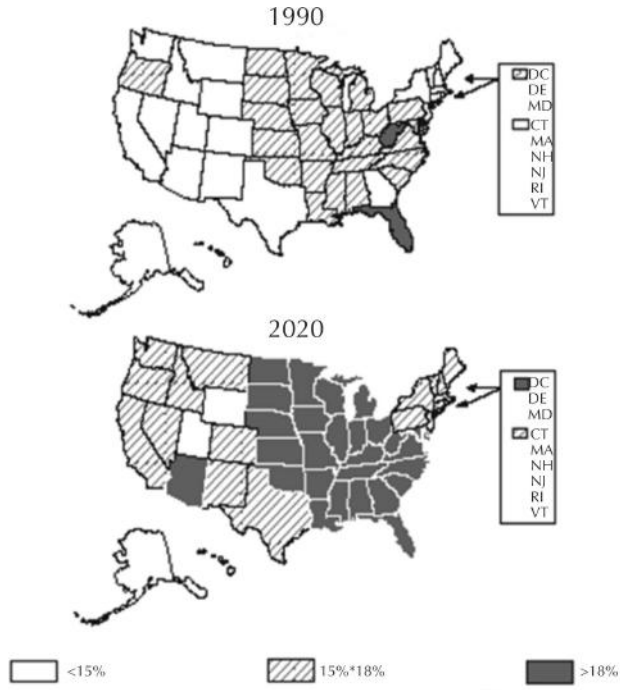

FIGURE 5 Estimated arthritis prevalence and projections (31).

9.4.3 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) involves inflammation in the lining of the joints and/or other internal organs, and is one of the most common forms of arthritis. RA typically affects many different joints and can affect the entire body. It is typically chronic that can last for a long time, and can be a disease of flareups. It is characterized by the inflammation of the membrane lining the joint, which causes pain, stiffness, warmth, redness and swelling. The inflamed joint lining – the synovium – can invade and damage bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement. Symptoms include inflammation of joints, swelling, difficulty in moving, joint pain, loss of appetite, fever, loss of energy, and enemia. These symptoms can affect other parts of the body.

Other features include lumps (rheumatoid nodules) under the skin in areas subject to pressure (e.g., back of elbows). Early in the disease, people may notice general fatigue, soreness, stiffness and aching. Pain and swelling may occur in the same joints on

both sides of the body and will usually start in the hands or feet. RA affects the wrist and many of the hand joints, but usually not the joints that are closest to the fingernails (except the thumb). RA also can affect elbows, shoulders, neck, knees, hips and ankles. It tends to persist over prolonged periods of time, and overtime-inflamed joints may become damaged. An advanced stage of RA in the hand joints with deformation damage is shown in Fig. 6. It is possible to see the inflammation in the joint of the fingers and the knuckles (28).

9.4.4 OSTEOARTHRITIS

Osteoarthritis (OA), or degenerative joint disease, is one of the oldest and most common types of arthritis. It is characterized by the breakdown of the cartilage. Cartilage is the part of the joint that cushions the ends of bones. Cartilage breakdown causes bones to rub against each other, causing pain and loss of movement (23). Most commonly affecting middle-aged and elderly persons, OA can range from very mild to very severe. It affects hands and weight-bearing joints such as knees, hips, feet and the back. Osteoarthritis usually and progress slowly. Early in the disease, the joints may ache after physical work or exercise.

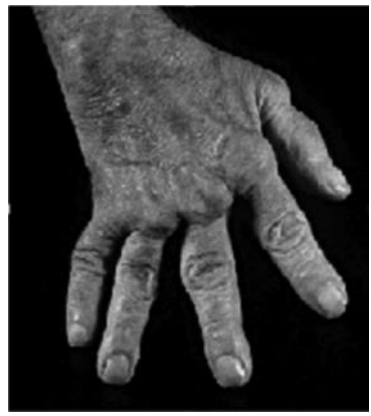

FIGURE 6 Hand with rheumatoid arthritis (7).

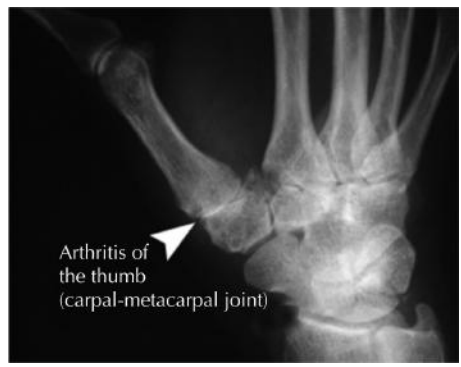

FIGURE 7 Osteoarthritis in the thumb (7).

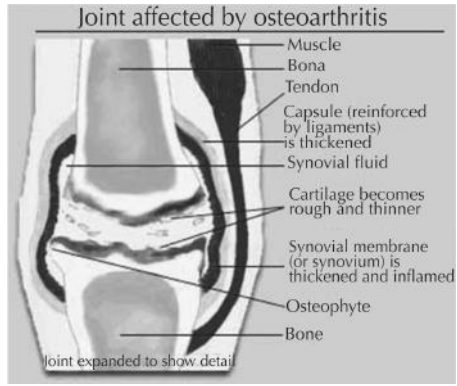

FIGURE 8 Joint affected by osteoarthritis (46).

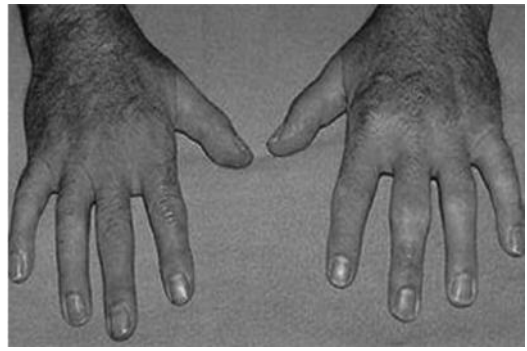

FIGURE 9 Psoriatic Arthritis swelling the fingers and affecting the skin on the hands (44).

Not everyone with OA feels pain. In fact, only one-third of patients have signs of pain or other symptoms. For those who do experience symptoms, the most common warning signs may include:

- Steady or intermittent pain in a joint.
- Stiffness that tends to follow periods of inactivity, such as sleep or sitting.
- Swelling or tenderness in one or more joints (not necessarily occurring on both sides of the body at the same time).
- Crunching feeling or sound of bone rubbing on bone (called *crepitus*), when the joint is used.

Although OA can occur in any joint, most often it occurs in the following areas (23 and 27):

- **Fingers:** OA of the fingers is often hereditary. More women than men have osteoarthritis of the fingers, especially after menopause. Small, bony knobs (called Heberden's nodes) appear at the end finger joints. Similar knobs (called Bouchard's nodes) can appear at the middle finger joints. Fingers can become enlarged and gnarled. They may ache or become stiff and numb. The base of the thumb joint is also commonly affected (Figs. 7 and 8).

- **Knees:** Because knees are primary weight-bearing joints, they are very commonly affected by OA. They may be stiff, swollen, and painful, making it hard to walk, climb, and get in and out of chairs and bathtubs. If OA of the knee is not treated, it can lead to disability.
- **Hip:** OA in the hip can cause pain, stiffness, and severe disability. The patient may feel the pain in the hips, groin, inner thigh, or knees. The person may have difficulty moving, bending, and walking. This can interfere with daily activities such as dressing and foot care.
- **Spine:** OA of the spine can cause stiffness and pain in the neck or in the lower back, and weakness or numbness in the arms or legs (23 and 27).

9.4.5 CRYSTAL DEPOSITION

At least three different calcium-containing crystals are now known to deposit in joints and to be associated with a variety of patterns of arthritis in the same way as ureate crystals cause the various features of gouty arthritis. Calcium pyrophosphate and occasionally calcium oxalate produce linear or punctuate calcifications in menisci and articular cartilage that can be readily seen on roentgenograms. These calcifications are termed chondrocalcinosis. Both these crystals and calcium apatite can also deposit diffusely in synoviurn and periarticular tissues, giving a soft tissue pattern on roentgenograms. X-rays may not show obvious calcifications when crystals are relatively few. Definitive diagnosis is made only by aspiration of synovial fluid for identification of the crystal type (26).

9.4.5.1 CALCIUM PYROPHOSPHATE DIHYDRATE CRYSTAL DEPOSITION DISEASE (CPPD OR PSEUDO GOUT)

CPPD Crystal is a joint disease caused by deposition of calcium pyrophosphate dihydrate crystals with protean manifestations that may include intermittent attacks of acute arthritis, a degenerative arthropathy that is often severe but can be asymptomatic, and X-ray evidence of calcification of the articular cartilage (chondrocalcinosis) in characteristic sites. The condition causes pain, redness, heat, and swelling in one or more joints. It is called Pseudo Gout or Chondrocalcinosis due to the weakening of the cartilage. It may cause it to break down more easily. The presence of these tiny CPPD crystals in the joints, and the reaction of a body to these crystals, create inflammation to attack the crystals. It is not known why these crystals are formed, however may be an abnormality in the cartilage cells or connective tissue. The cause may also be a genetic (26 and 39).

9.4.6 INFECTIOUS ARTHRITIS

Infectious arthritis is a form of joint inflammation caused by a germ. The germ can be a bacterium, a virus or a fungus. Infectious arthritis is not transmittable from one person to the other, but some germs (such as those causing gonorrhea and measles) can be spread by person-to-person contact. However, while these diseases can be passed on, this does not automatically mean the development of infectious arthritis (21). Infection of the joints usually occurs after a previous infection elsewhere in the body. Infectious arthritis causes pain and swelling in the joints. There is usually only one joint involved, though sometimes two or three joints can become infected. Mostly,

infectious arthritis affects the large joints (shoulders, hips, knees), but smaller joints (fingers, ankles) can also be involved. It does not usually last a long time if it is treated early. Any person, at any age, can get infectious arthritis. However, some people are more likely to get infectious arthritis than others. These include those with conditions that make it difficult to fight off infection, such as:

- Diabetes.
- Sickle-cell anemia.
- Severe kidney disease.
- AIDS.
- Immune deficiency.
- Some forms of cancer.
- Alcoholism.
- Intravenous drug abuse.

People with an existing arthritis are also more likely to develop infectious arthritis, because germs tend to infect the damaged joint that is weaker than a healthy joint. Infectious arthritis can also develop in a patient with a surgery of a joint, and it usually happens a short time after the surgical procedure. Some of the stronger medications used to treat certain types of inflammatory arthritis can also lower the resistance of the joint to infection, making it easier for infectious arthritis. There is a good chance of contracting infectious arthritis in people who work in jobs where exposure to animals, plants, marine life and soil.

The symptoms of infectious arthritis vary according to the type of germ causing it. If the arthritis is caused by a bacterium, inflammation is generally located in only one place or area. The infection is often accompanied by fever and chills and its onset is quite sudden. With infectious arthritis caused by a virus, there is usually no fever, but there is an aching feeling all over the body. Inflammation caused by a fungal infection can be in one area or throughout the body, and it usually occurs very slowly, over weeks or months. One may have a mild fever or no fever at all. Bacteria cause most cases of infectious arthritis. The types of bacteria that might cause such infection include:

- Gonococcus.
- Staphylococcus.
- Streptococcus.
- Pneumococcus.
- Hemophilus.
- Spirochetes.
- Tuberculosis.

Certain viruses can also cause infectious arthritis, such as:

- Infectious hepatitis.
- Mumps.
- Infectious mononucleosis.

Fungi are the least common cause of infectious arthritis, and these are usually found in:

- Soil.
- Bird droppings.

- Certain plants, such as roses.

9.4.7 PSORIATIC ARTHRITIS

Psoriatic arthritis is a specific type of arthritis. It causes inflammation in and around the joints, usually the wrists, knees, ankles, lower back and neck. Psoriatic arthritis is a specific type of arthritis that has been diagnosed in approximately 23 percent of people who have psoriasis, according to the Psoriasis Foundation's 2001 Benchmark Survey. It commonly affects the ends of the fingers and toes. It can also affect the spine. The disease can be difficult to diagnose, particularly in its milder forms and earlier stages. Early diagnosis, however, is important for preventing long-term damage to joints and tissue. Most people with psoriatic arthritis also have psoriasis. Rarely, a person can have psoriatic arthritis without having psoriasis. The symptoms of psoriatic arthritis are:

- Stiffness, pain, swelling and tenderness of the joints and surrounding soft tissue
- Reduced range of motion
- Morning stiffness and tiredness
- Nail changes, including pitting (small indentations in the nail) or lifting of the nail—found in 80 percent of people with psoriatic arthritis
- Redness and pain of the eye, similar to conjunctivitis

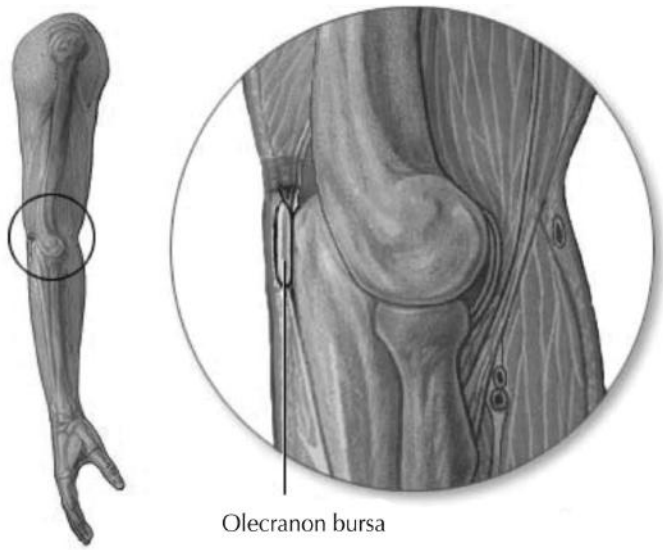

FIGURE 10 Bursa of the elbow **(40).**

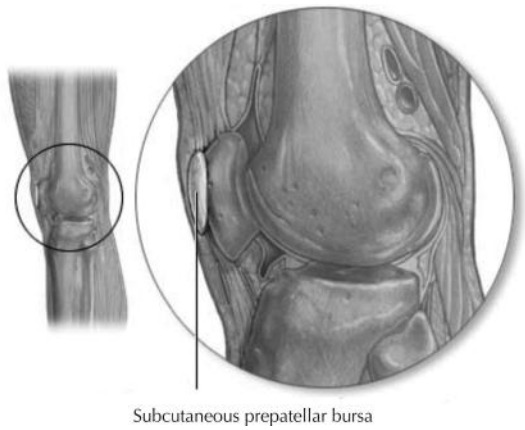

FIGURE 11 Bursa of the knee **(40).**

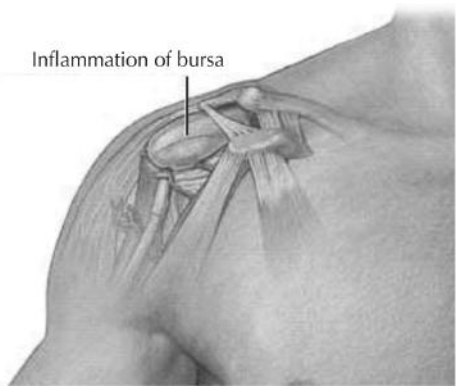

FIGURE 12 Bursitis of the shoulder **(40).**

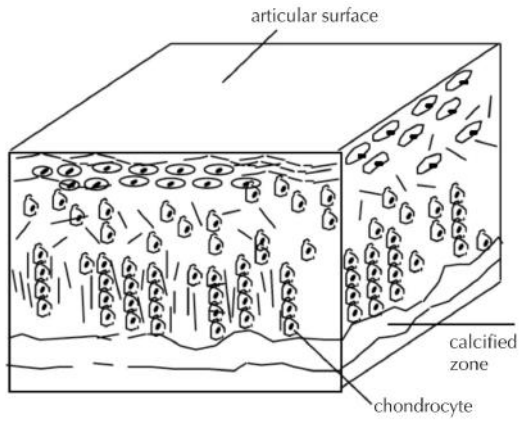

FIGURE 13 Articular surface calcified zone chondrocyte. Illustration of the organization of articular cartilage. Chondrocytes make up less than 10% of cartilage volume. Collagen fibers are arranged parallel to the articular surface in the outer zone and perpendicular to the surface in the deep zone (8).

Psoriatic arthritis can develop at any time. On average, it appears about 10 years after the first signs of psoriasis. For most people it appears between the ages of 30 and 50. It affects men and women equally. In about one of seven people with psoriatic arthritis, arthritis symptoms occur before any skin lesions. Like RA, psoriatic arthritis may be caused by a malfunctioning of immune system. Psoriatic arthritis is usually milder than RA, but some patients with psoriatic arthritis have as severe disease as patients with RA. Psoriatic arthritis can start slowly with mild symptoms, or it can develop quickly. It is very important to have an accurate diagnosis. Left untreated, psoriatic arthritis can be a progressively disabling disease. In fact, half of those with psoriatic arthritis already have bone loss by the time the disease is diagnosed.

The Fig. 9 presents psoriatic arthritis in the hands. It is possible to see that the hands are inflammated, specially the hand in the right side of the picture, which has inflammation in the area of the fingers and the area of the knuckles (44).

9.4.8 BURSITIS

Bursitis is inflammation of the fluid-filled sac (bursa) that lies between a tendon and skin, or between a tendon and bone. Figures 10 and 11 show the locations of the bursa of the elbow and the bursa of the knee, respectively. The condition may be acute or chronic. Bursitis simply is the inflammation of a bursa. In the normal state, the bursa provides a slippery surface that has almost no friction. A problem arises when a bursa becomes inflamed. The bursa loses its gliding capabilities, and becomes more and more irritated when it is moved. When the condition bursitis occurs, the slippery bursa sac becomes swollen and inflamed. The added bulk of the swollen bursa causes more friction within already confined spaces. Also, the smooth gliding bursa becomes gritty and rough. Movement of an inflamed bursa is painful and irritating. Figure 12 shows the inflammation of the bursa in the shoulder leading to bursitis. Bursitis usually results from a repetitive movement or due to prolonged and excessive pressure. Patients who rest on their elbows for long periods or those who bend their elbows frequently and repetitively (e.g., a custodian using a vacuum for hours at a time) can develop elbow bursitis, also called olecranon bursitis. Similarly in other parts of the body, repetitive use or frequent pressure can irritate a bursa and cause inflammation. Other causes of bursitis include traumatic injuries and systemic inflammatory conditions. Following trauma, such as a car accident or fall, a patient may develop bursitis. Usually a contusion causes swelling within the bursa. The bursa, which had functioned normally up to that point, now begins to develop irritation with what were normal movements and activities. This can lead to bursitis. Systemic inflammatory conditions, such as RA, may also lead to bursitis. These types of conditions predispose patients to develop the inflammation of a bursa (40). The symptoms of bursitis are:

- Joint pain and tenderness.
- Swelling.
- Warmth over the affected joint.

9.4.9 SYNOVITIS

Synovitis is an inflammation of the synovial membrane. Synovitis also refers to an inflammation of the synovial lining of a joint as opposed to a bursal wall (bursitis)

or tendon sheath (tenosynovitis). Types of synovitis are: fibrinous, gonorrheal, tuberculous and rheumatic, among others. With most imaging methods, including routine radiography and CT, the differentiation of synovial inflammatory tissue and joint fluid is not possible. MR imaging can provide additional information regarding the extent of synovial disease. Specifically, the intravenous administration of a gadolinium compound allows distinction between effusion and abnormal synovium, with the effusion remaining of low signal intensity and the synovium demonstrating enhancement and increased signal intensity on T1-weighted spin-echo MR images obtained immediately after the injection. However, a delayed enhancement of joint fluid after intravenous administration of a gadolinium chelate is well documented.

MR imaging in cases of synovitis can show intrasynovial regions of low signal intensity representing fibrous bodies (rice bodies). In cases of pigmented villonodular synovitis or idiopathic synovial (osteo) chondromatosis, diagnostic MR imaging abnormalities may be seen due to the presence of haemosiderin deposition (in pigmented villonodular synovitis) or cartilage nodules (in idiopathic synovial: osteochondromatosis).

Two forms of proliferative disorder of the synovial membrane are villonodular synovitis and pigmented villonodular synovitis. The normal synovium is only a few cells thick and therefore not visible on imaging. With inflammation of the synovium, synovial fluid accumulates to form a joint effusion. If the inflammation is chronic, the synovium itself may become hypertrophied.

Conventional radiographs may suggest a joint effusion or synovial hypertrophy as an increased soft tissue density adjacent to the joint surface. If the synovitis is secondary to recurrent hemorrhage or pigmented villonodular synovitis haemosiderin deposition may further increase this soft tissue density. Radiographs are not capable of differentiating synovial fluid from synovial hypertrophy.

Ultrasound is a sensitive method of detecting a joint effusion and will readily differentiate fluid from synovial hypertrophy even if echoes are present within the synovial fluid. Fluid may be balotted away from the field of view by increased transducer pressure whereas synovium is relatively noncompressible. Ultrasound will not reliably differentiate infection from non infective causes of synovitis as fluid may contain echoes with either. Ultrasound does facilitate fluid aspiration for bacteriological analysis. Ultrasound also allows guidance for synovial biopsy if required.

MR imaging is usually able to differentiate synovial fluid from synovial hypertrophy particularly on T2-weighted sequences. Intravenous gadolinium-DTPA contrast enhancement enables differentiation of synovial fluid from synovial hypertrophy on T1-weighted or fat suppressed T1-weighted sequences using short scan times. Synovial fluid will indicate low signal whereas synovial hypertrophy shows a contrast enhancement. However, if more than five minutes elapse between injection and image acquisition, then gadolinium DTPA may leak into the synovial fluid increasing its signal due to paramagnetic effects. Dynamic contrast enhancement curves may be obtained for specific regions of interest if short temporal resolution sequences are obtained over a period of two to three minutes post gadolinium DTPA injection.

MR imaging may also help demonstrate the etiology for synovitis. In synovitis due to infection, the more proteinaceous nature of the synovial fluid causes increased

signal on T1-weighted images. If the hypertrophied synovium contains haemosiderin secondary to hemorrhage then T2*-gradient echo sequences accentuate the signal void from the haemosiderin deposits. Radionuclide bone scans are sensitive for demonstrating synovitis both during the blood pool and soft tissue phases due to hyperaemia and also during the bone phase due to local alterations in bone activity. Scintigraphy is particularly good for assessing multiple joints in systemic inflammatory arthritis, provided the disease is asymmetrical (16 and 41).

Toxic synovitis is a frequent cause of limping with hip pain in children. It occurs in children prior to the onset of puberty and is a transient arthritis of the hip that usually resolves on its own. Its cause is not known but boys are affected more frequently than girls (approximately 4 to 1). Symptoms are usually mild and generally include hip pain and a slight limp. The hip pain almost always involves only one side (unilateral). A low grade fever (usually less than 1010F) may be an early symptom. Aside from the hip discomfort, the child does not usually appear ill. Toxic synovitis is a diagnosis of exclusion: Once these other diagnoses have been excluded, then the diagnosis of toxic synovitis (which is the most common of all these diseases) is usually made (16). In children, there are three potentially serious diseases that can cause hip pain and limp: septic hip, slipped capital femoral epiphysis, and Legg-Calve-Perthes disease. The symptoms related to toxic synovitis are:

- Hip pain (on one side only).
- Limp.
- Thigh pain, in front and toward the middle (may be present).
- Knee pain (may be present).
- Low grade fever, less than 1010F (may be present).

Some of the tests to detect synovitis signs are:

- Ultrasound of the hip will demonstrate a joint effusion.
- X-ray of the hip (expected to be normal).
- ESR may be slightly elevated.
- Complete blood count (may show increased white cells).

Other tests are occasionally conducted to rule out other causes of hip pain:

- Aspiration of fluid from the hip joint.
- Bone scan.
- MRI.

9.5 JOINT ARTICULAR CARTILAGE: COMPOSITION AND BEHAVIOR

Cartilage and bone are specialized connective tissues composed of roughly the same material: cells embedded in an extracellular matrix, permeated by a network of fibers. During the early part of fetal life a large part of the human skeleton is cartilaginous, but with age most of the cartilage is mineralized to bone. In the adult, cartilage remains on articulating surfaces of synovial joints, in the larynx, thorax, bronchi, nose, and ears. The discussion here is limited to articular or hyaline cartilage, which covers the ends of all bones in synovial joints. The fibrocartilage and elastic cartilage found in other locations of the body (e.g., intervertebral disks and ear respectively) will not be considered in this chapter. Hyaline cartilage is the most abundant of the three types of

cartilage. None of the cartilage types have intrinsic blood vessels, nerves, or lymph vessels.

The articular cartilage in diarthrodial joints increases the area of load distribution and provides a smooth wear resistant surface. Therefore, cartilage is very good at distributing loads and providing lubrication for joints. It appears that proteoglycans provide compressive strength. In fact the loss of compressive strength that occurs in response to various diseases can be attributed to a reduction in the proteoglycans content. Cartilage is often considered to be a biphasic material consisting of a solid phase and a fluid phase. The interaction of these two phases gives rise to the mechanical behavior of cartilage. Cartilage is not well suited for self repair. Damage to cartilage may disrupt the normal load carrying ability of the tissue and thus the normal lubrication process. Further loading of damaged cartilage may lead to osteoarthritis (8).

9.5.1 STRUCTURE

Cartilage consists of two distinct phases: a fluid phase composed of water and electrolytes, and a solid phase consisting of collagen fibrils (primarily type II collagen), proteoglycans, and other glycoproteins. Articular cartilage is composed of 68–85% water, 10–20% collagen, and 5–10% by wet weight of proteoglycans. Chondrocytes (cartilage cells) manufacture collagen and proteoglycans, which are then assembled outside the cell into a mesh of collagen interwoven with aggregated proteoglycan molecules called aggrecan. Chondrocytes do not have a blood supply so they must receive their nutrients through the synovial fluid. Chondrocytes are encapsulated in a bag surrounded by the viscoelastic extracellular matrix. The chondron consists of the chondrocyte, the bag surrounding it, and the fluid contained within the bag. The mechanical properties of cartilage depend on the extracellular matrix, but the existence and maintenance of the matrix depends on chondrocytes. The content and structure of collagen and proteoglycans vary as a function of the depth from the articulating surface. Cartilage can be viewed as having three separate zones. The outer 10–20% layer contains fine collagen fibrils arranged parallel to the surface. In the middle 40–60% zone the collagen fibers are arranged more randomly. In the deep zone the collagen fibers are woven together and aligned perpendicular to the articulating surface (Fig. 13). The thickness of articular cartilage varies with species, the particular joint, and the location within the joint. Generally it ranges from 0.5 mm in rabbit knee joints, to 1.0 mm in the patellofemoral grove of bovine knee joints, to 1.5 mm in the human patella. Interactions take place between the fluid, proteoglycan molecules and various electrostatic charges. Proteoglycans are hydrophilic (attract water). There are electrostatic attractions between the positive charges along the collagen molecules and the negative charges that exist along the glycosaminglycans. Chondroitin 4-sulfate, chondroitin 6-sulfate, and keratin sulfate are the three predominate GAGs found in cartilage. Proteoglycan molecules repel each other if forced together (Fig. 14). Hydrostatic forces develop as cartilage is deformed and fluid tries to move throughout the tissue. Proteoglycans are placed in tension during cartilage loading as they attempt to restrain water flow. It is the combined effect of all these interactions that give rise to the mechanical properties of the material (8).

9.5.2 MATERIAL PROPERTIES

Like bone, the properties of cartilage are anisotropic. The anisotropy results in part from the structural variations described above. Cartilage is a viscoelastic material. Because of its structure (Figs. 13 and 14), cartilage is rather porous allowing fluid to move in and out of the tissue. If the tissue is subjected to a compressive stress, then fluid flows out of the tissue. Fluid returns when the stress is removed. The material properties of cartilage change with its fluid content, thus making it important to know the stress-strain history of the tissue to know its load carrying capacity. The mechanical properties also change as a function of location within the cartilage and pathology. The compressive aggregate modulus for human articular cartilage is correlated inversely with the water content and directly with proteoglycan content per wet weight (Fig. 15). There is no correlation with the collagen content thus suggesting that proteoglycans are responsible for the tissue's compressive stiffness. It is difficult to conduct the tests on cartilage because it is rarely over one mm thick and it overlays highly curved bony surfaces. The indentation test is most common mechanical test performed on cartilage. During this test, a load is applied to the surface of the cartilage and the creep is recorded. When the load is then removed, an instantaneous recovery is followed by a time-dependent behavior. It is interesting that the tissue will recover fully if completely submerged in a solution bath, but will not recover if it is exposed to air. Other common tests conducted on cartilage are tensile tests and shear tests. Because of anisotropy of the tissue, it elicits different behavior relative to each of these tests (8).

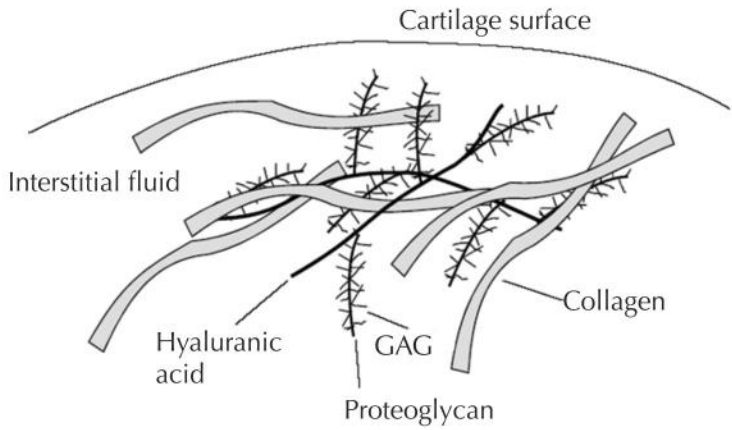

FIGURE 14 Illustration of the constituents of cartilage and their arrangement: Collagen molecules provide tensile strength. Glycosaminoglycans (GAGs) are negatively charged and repel each other. Proteoglycans are hydrophilic and attract water. If a compressive load is applied to the articular surface, then fluid flows out of the cartilage due to the membrane permeability (8).

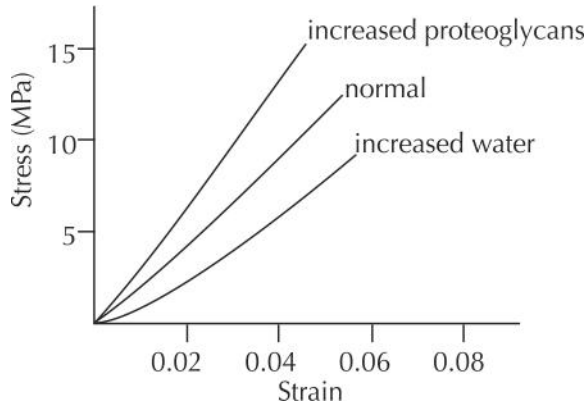

FIGURE 15 The effect of water content and proteoglycan concentration on the tensile properties of cartilage (8).

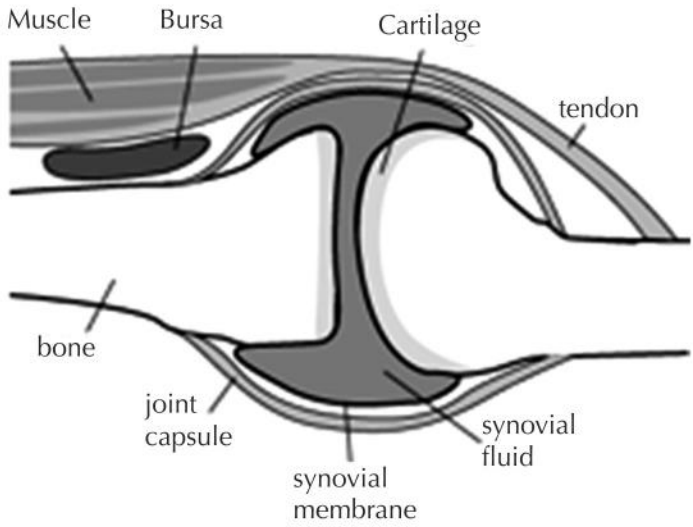

FIGURE 16 Schematic Diagram of a joint (8).

9.5.3 LOADING OF CARTILAGE

Articular cartilage is routinely subjected to a variety of loads, but the most common loads are compression, torsion and shear. As stated above the ability of the tissue to withstand these loads depends on its past stress-strain history and its composition (8). Mechanical properties of the human cartilage are compared with other body tissues in Table 2.

9.5.4 JOINT FRICTION/LUBRICATION

Articular cartilage has exceptional lubricating properties and low coefficient of friction that greatly assist its function in synovial joints. Its coefficient of friction is almost

two orders of magnitude less than most oil lubricated metal on metal surfaces. There are four possible lubricating mechanisms that could contribute to this low coefficient of friction: boundary, hydrostatic, hydrodynamic, and elastohydrodynamic. For each of these mechanisms, the lubricant is assumed to be **synovial fluid**.

In boundary lubrication, the lubricant is simply absorbed onto a rough surface to make it act smoother. Hydrostatic lubrication refers to the pressurization of lubricant between two or more surfaces. This is a common type in industrial application with pressurized bearings. This type does not appear to exist in diarthrodial joints. "Hydrodynamic Elastohydrodynamic" theory assumes that as cartilage deforms under load some fluid is expelled and the lubrication is due to the support of a moving bearing by a wedge of fluid (e.g., a hydroplane that skims across the trapped between the articulating surfaces). This fluid could then act in a hydrodynamic way by forming a wedge or in a hydrostatic way as further load is applied to pressurize the fluid. It is believed that this type of lubrication, which really is a combination of the other three types, probably approximates what actually occurs within a joint. In Fig. 16, we can observe more clearly the location of the synovial fluid that plays an important role in the lubrication of a joint (8).

9.6 LUBRICATION MECHANICS

Many flows within the body occur between surfaces that are very close to each other compared with their lateral extents. Examples are flow of synovial fluid within joints in the musculoskeletal system. Lubrication of joints is remarkable in that very large forces normal to joint surfaces can be sustained even though tangential forces acting on those surfaces are small. The former arise primarily from the very high pressure sustained in the lubricating fluid layer, while the latter are due to viscous friction. Thus, the analysis of lubrication theory is based on the determination the surface pressure and fluid velocity.

The two-dimensional steady flow of an incompressible fluid is considered in Cartesian coordinates. For equilibrium between the pressure term and the viscous stress term in the *x*-direction, the reference pressure must be: $P=\mu UL/h^2$. Neglecting the terms multiplied by h/L and $(h/L)^2$, the resulting equations of motion are shown in Eq. (1). The *y*-component of velocity is $v_y << v_x$ and can be neglected. The pressure varies only in the *x* direction. Let us consider a flow between two surfaces: a lower surface that is stationary horizontal plane and an upper surface given by $y = h(x)$ and all of whose points move with velocity U in the *x* direction. For simplicity, we shall restrict this analysis to a case with no movement of the upper surface in the *y* direction. For the boundary conditions defined in Eq. (2) and for a Newtonian fluid, the solution for Eq. (1) is shown in Eq. (3). The integration of the velicity Eq. (3) will yield the volumetric fluid flux as shown in Eq. (4).

$$\frac{\partial p}{\partial x} = \frac{\partial}{\partial y}\left(\mu \frac{\partial u_x}{\partial y}\right), \text{ and } \frac{\partial p}{\partial y} = 0 \tag{1}$$

$$v_x = 0 \quad y = 0, \text{ and } v_x = U \quad y = h \tag{2}$$

$$v_x = \frac{1}{2\mu}\frac{dp}{dx}\left[y\left(y-h\right) + U\frac{y}{h} \right] \tag{3}$$

$$Q_x = \int_0^{h(x)} v_x dy = -\frac{h^3}{12\mu}\frac{dp}{dx} + \frac{Uh}{2} \tag{4}$$

$$0 = \int_0^{h(x)} \frac{dv_x}{dx} dx = \frac{d}{dx}\int_0^{h(x)} v_x dx - v_x(x,h)\frac{dh}{dx} = \frac{dQ_x}{dx} - U\frac{dh}{dx} \tag{5}$$

$$\frac{1}{\mu}\frac{d}{dx}\left(h^3\frac{dp}{dx} \right) = -6U\frac{dh}{dx} \tag{6}$$

$$\frac{1}{\mu}\frac{d}{dx}\left(h^3\frac{dp}{dx} \right) = 6\left[h\frac{dU}{dx} - U\frac{dh}{dx} + 2V \right] \tag{7}$$

We now integrate the continuity Eq. (4) over the thickness of the lubrication layer for $v_y \approx 0$. We also use "Leibnitz's rule" for differentiating an integral as shown in Eq. (5). Combining Eqs. (4) and (5), we get Eq. (6) that is a Reynolds equation for lubrication mechanics. A more general form of the Reynolds equation that allows for the velocity (V, *y*-component) of the upper surface and that also allows U and V to vary with *x* is shown in Eq. (7).

Knowing $h(x)$, $U(x)$, and $V(x)$, and the boundary conditions for pressure at upstream and downstream ends of the flow region, the Eq. (7) can be solved for the pressure variation, $p(x)$. The net normal (lubricating forces on the upper and lower surfaces) can then be readily obtained by multiplying the pressure with the surface area. These equations are applicable to the lubrication of diarthrodial joints within the body. Such biological lubrication is a biomechanically sophisticated and complex phenomenon. The lubricating fluid is the synovial fluid, a dialysate of blood plasma, which contains a small cellular component and hyaluronic acid, a long-chain polymer that is found at many places within the body.

Structurally, the presence of the hyaluronic acid is like a network of macromolecules, the interstices of which are filled by a low-viscosity fluid. The presence of hyaluronic acid in the synovial fluid gives rise to complex rheological behavior, including shear thinning. Overall, the lubrication mechanism in diarthrodial joints depends not simply upon the properties of synovial fluid, but also upon the roles of the adyacent cartilage and other mechanisms.

9.7 SYNOVIAL FLUID

The synovial fluid is a thick, clear lubricant (made mostly of carbon dioxide and some nitrogen) found between the bones, in the body cavities (42). Table 2 shows the physical properties and chemical composition of the human synovial fluid. Table 3 shows the synovial fluid characteristics by degree of inflammation.

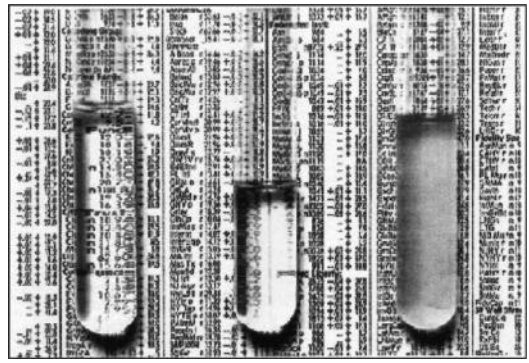

FIGURE 17 Appearance of the synovial fluid. Left: Synovial fluid is a normal synovial fluid. Center synovial fluid is an inflammatory synovial fluid. Right: Synovial fluid is opaque, sensitive for fracture (42).

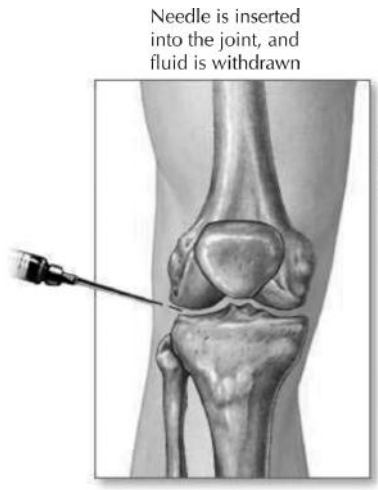

FIGURE 18 Sampling of synovial fluid for analysis (42): The needle is inserted into the joint to withdraw the fluid.

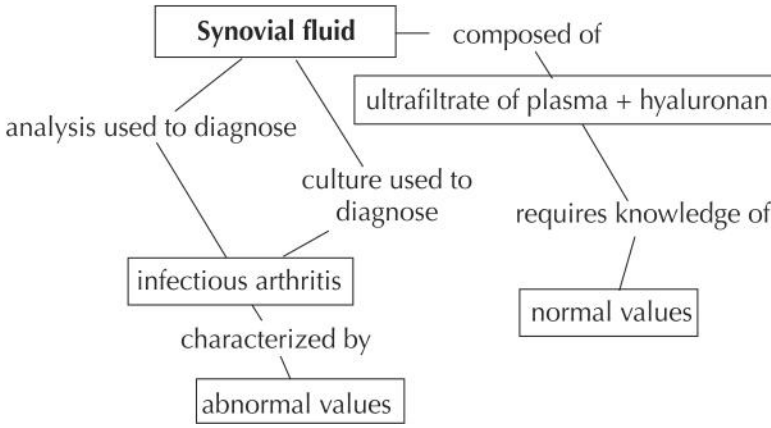

FIGURE 19 Flow diagram for analysis of synovial fluid (42).

TABLE 2 Physical properties and chemical composition of human synovial fluid (1:329–330).

Property or Constitutent	Units	Value
Physical Properties		
pH	—	7.39
Specific Gravity	—	(1.008–1.015)
Viscosity, intrinsic	—	46.3
Volume	mL	1.1
General Chemical Components		
Leukocytes:		
Total	cells/mm^3	63
Polymorphonuclear	%	6.5
Clasmatocytes	%	10.1
Lymphocytes	%	24.6
Monocytes	%	47.9
Synovial Cells	%	4.3
Unclassified		
Phagocytes	%	4.9
Unidentified Cells	%	2.2
Solids, total	g/100 g	3.41
Electrolytes		
Calcium	mg/100 ml	9.7
Carbon Dioxide	vol %	57.1
Potassium	mEq/L	4.0
Sodium	mEq/L	136.1
Nitrogenous Substances		

TABLE 2 *(Continued)*

Property or Constitutent	Units	Value
Protein, total	g/100 mL	1.72
	g/100 mL	2.80
Albumin	g/100 mL	1.02
	g/100 mL	1.89
Globulin	g/100 mL	0.05
	g/100 mL	0.91
Uric Acid	mg/100 mL	3.90
Nitrogen:		
Total N	g/100 mL	0.88
Non-protein N	mg/100 mL	32.40
Mucin N	mg/100 mL	104.00
Carbohydrates, Miscellaneous Organic Acids		
Glucosamine, Mucin	mg/100 mL	87.0
Sugar	mg/100 mL	96.4
Hyalonuric Acid	mg/100 mL	157.0
Lactic Acid	mg/100 mL	20.5
Sialic Acid	mg/100 mL	28.0

Synovial Fluid Volume and Appearance (Fig. 17)

A. **Normal synovial fluid:**	B. **Inflammatory fluid:**	C. **Findings suggestive of acute fracture or derangement:**
1. Slightly yellow, straw colored. 2. Clear (Can read newsprint through the fluid). 3. Viscous consistency and no clotting	1. Yellow green to gray. 2. Cloudy to Opaque. 3. Decreased viscosity to watery consistency.	1. Large fat droplets (sensitive for fracture). 2. Bloody fluid.

9.7.1 SYNOVIAL FLUID EXAMINATION

Synovial fluid analysis is a battery of tests performed on synovial (joint) fluid to help diagnose and treat joint-related abnormalities (42). To obtain the fluid for analysis, a sterile needle is inserted into the joint space through skin that has been specially cleaned. Once in the joint, fluid is aspirated through the needle into a sterile syringe (Fig. 18). Synovial fluid is normally a viscous (thick), straw colored substance found in small amounts in joints, bursae, and tendon sheaths. In the laboratory, the fluid is initially analyzed for color and clarity. It is then examined microscopically for cells (red and white cells), crystals (in the case of gout), and bacteria. In addition, there may be a chemical analysis, and if infection is a concern, a sample will be cultured to see if any bacteria grow. Figure 19 shows a simplified flow diagram for the analysis of the synovial fluid. The Tables 4 and 5 show the effect of joint diseases on synovial fluid and the variation in chemical composition in the synovial fluid due to joint diseases,

respectively. The Tables 3 to 5 can be used as a guide for the examination of the synovial fluid. Typically an abnormal joint fluid may look cloudy or abnormally thick. This depends on the joint disease or condition (42).

TABLE 3 Joint fluid characteristics by degree of inflammation (34).

Normal synovial fluid	**Little inflammation: traumatic arthritis and osteoarthritis**	**Moderate inflammation: most "inflammatory" arthritic diseases**	**Severe Inflammation: Possible septic arthritis**
Very high viscosity	High viscosity	Low viscosity-runny	Runny
Volume low	Volume moderate	Volume moderate/high	Volume high
Color – straw	Straw	Straw to opalescent	Variable. Greenish/ khaki.
Clarity – transparent	Transparent	Translucent/opaque	Opaque
Firm mucin clot	Firm mucin clot	Friable	Friable
WBC/ml < 10^5	WBC/ml 10^5–10^6 *	WBC/ml* 10^6–10^8	WBC/ml** 10^6–10^8
< 25% PMN	< 25% PMN	> 50% PMN often	> 75%PMN
Few/no ragocytes	Few/no ragocytes	> 60% ragocytes often	> 95% ragocytes

Key: WBC = white cell count/ml; PMN = polymorphonuclear leucocyte cells;

Ragocytes = phagocytic cells containing distinctive "larger than normal" granules.
*Approximate values**.** ** May be lower with low virulance organisms, or if partially treated.

TABLE 4 Effects of joint diseases on the cellular content of the synovial fluid (1:335).

Condition	**Gross Appearance**	**Clot**	**Erythrocytes per cu mm**	**Leukocytes**			
				Total per cu mm	**Poly morpho-nuclear %**	**Lym-pho-cytes %**	**Mono-cytes %**
Normal	Clear	0	160 (0–2000)	63 (13–80)	7 (0–25)	25 (6–78)	63 (0–71)
Arthritis Gouty	Turbid	1.6(0–4)	54,000 (0–616,000)	13,300 (1,000–70,000)	71 (0–99)	8 (0–43)	21 (1–79)
Rheumatoid	Clear to turbid	0.5(0–3)	4,000 (0–75,000)	14,000 (450–75,000)	65 (0–96)	20 (0–92)	15 (0–97)
Specific infectious	Very turbid	1.4(0–3)	34,000 (0–148,000)	73,370 (7,800–266,000)	90 (46–100)	3 (0–19)	7 (0–44)
Traumatic	Clear to slightly turbid	0.3(0–1)	2,190 (0–15,650)	1,320 (50–10,400)	5 (0–36)	36 (0–88)	59 (8–83)
Traumatic with hemorrhage	Red	0.6(0–2)	1,305,000 (20,000–6,500,000)	1,540 (100–7,500)	17 (0–77)	28 (0–88)	50 (6–95)

TABLE 4 *(Continued)*

Condition	Gross Appearance	Clot	Erythrocytes per cu mm	Leukocytes			
				Total per cu mm	Poly morpho-nuclear %	Lym-pho-cytes %	Mono-cytes %
Tuberculosis	Turbid	0.6(0–3)	28,300 (50–229,000)	73,400 (2,500–105,000)	60 (18–96)	20 (3–49)	19 (0–62)
Degenerative joint disease	Clear to slightly turbid	0.6(0–2)	11,930 (0–169,000)	720 (70–3,600)	7 (0–58)	37 (4–86)	56 (7–100)
Lupus erythemato-sus disseminatus	Clear to turbid	0.1(0–2)	38,490 (0–336,000)	2,860 (100–18,200)	5 (0–32)	30 (0–84)	61 (0–100)
Pigmented villinodular synovitis	Turbid	0.8(0–3)	682,000 (29,000–2,724,000)	3,100 (400–11,000)	26 (2–61)	33 (12–64)	40 (12–65)
Rheumatic fever	Slightly turbid to turbid	1.1(0–3)	65,000 (0–740,000)	17,800 (300–98,200)	50 (2–98)	11 (0–38)	36 (0–88)

9.8 SEROUS FLUIDS

Serous fluids are the fluids contained within the closed cavities of the body. These cavities are lined by a contiguous membrane, which forms a double layer of mesothelial cells, called the serous membrane. The cavities are the pleural (around the lungs), pericardial (around the heart), and peritoneal (around the abdominal and pelvic organs) cavities. The main role of the Serous fluid is to lubricate the membrane and reduce the friction and abrasion when organs in the thoracic or abdominopelvic cavity move against each other or the cavity wall. The fluids are ultrafiltrates of plasma secreted by the epithelium, which are continuously formed and reabsorbed, leaving only a very small volume within the cavities. An increased volume of any of these fluids is referred to as an effusion.

TABLE 5 Effect of joint diseases on the chemical composition of the synovial fluid (1:335).

Condition	Protein, Total g/100 mL	Albumin g/100 mL	Globulin g/100 mL	Sugar Difference mg/100 mL	Mucin Precipitation
Normal	1.72(1.07–2.13)	1.02	0.05	0(0–10)	4
Arthritis Gouty	4.2(2.8–5.0)	2.7(1.4–3.4)	1.5(0.9–2.1)	10(0–50)	2(1–4)
Rheumatoid	5.0(3.8–809)	2.8(2.1–3.7)	2.2(1.2–3.3)	26(14–87)	2(1–4)
Specific infectious	4.8(2.9–6.9)	2.7(2.9–6.9)	1.6(1.5–3.8)	71(40–122)	1(1–4)
Traumatic	3.90(2.96–5.05)	3.22(2.65–4.04)	0.93(0.66–1.39)	5(0–10)	4(3–4)

TABLE 5 *(Continued)*

Condition	Protein, Total g/100 mL	Albumin g/100 mL	Globulin g/100 mL	Sugar Difference mg/100 mL	Mucin Precipitation
Traumatic with hemorrhage	3.88(2.85–5.45)	2.81(2.31–3.48)	1.16(0.59–2.02)	12(8–44)	3(2–4)
Tuberculosis	5.3(4.0–6.0)	3.3(2.8–4.3)	2.0(1.2–2.8)	60(8–108)	2(1–4)
Degenerative joint disease	3.08(1.29–4.87)	2.51(1.66–4.87)	0.75(0.33–1.36)	0(0–10)	4(2–4)
Lupus erythematosus disseminatus	2.51(1.52–3.78)	1.41(1.11–2.10)	1.15(0.62–1.68)	22(7–24)	4
Igmented villinodular synovitis	4.2(3.7–4.6)	2.9(2.7–3.2)	1.3(1.0–1.5)	22(0–50)	3(1–4)
Rheumatic fever	3.7(1.6–4.9)	2.4(1.2–3.0)	1.1(0.3–1.90)	10(5–50)	4(3–4)

Pleural fluid is normally present at about 1 to 10 mL, moistening the pleural surfaces. If inflammation occurs, the plasma protein drops, congestive heart failure is present, OR if there is decreased lymphatic drainage, there can be an abnormal accumulation of pleural fluid.

TABLE 6 Transudate versus inflammatory (exudate) values of the properties of the serous fluid (49).

Property	Transudate	Exudate
Appearance	Clear or yellow	Cloudy
Specific Gravity	<1.015	>1.015
Total Protein	<3.0 g/dl	>3.0 g/dl
Fluid Protein: Serum Protein Ratio	<0.5	>0.5
Lactic Dehydrogenase (LDH)	<200 IU	>200 IU
Fluid LDH:Serum LD Ratio	<0.6	>0.6
WBC Count	<1000/ul	>1000/ul
RBC Count	0-low	High
Spontaneous Clotting	No	Possible

The pericardial space enclosing the heart normally contains about 25 to 50 mL of a clear, straw-colored ultrafiltrate of plasma, called pericardial fluid. When an abnormal accumulation of pericardial fluid occurs, it fills up the space around the heart and can mechanically inhibit the normal action of the heart. In this case, immediate aspiration

of the excess fluid is indicated. Normally, less than 100 mL of the clear straw-colored fluid is present in the peritoneal cavity. An abnormal accumulation of the fluid is indicated by severe abdominal pain and may be caused by a ruptured abdominal organ, hemorrhage resulting from trauma, postoperative complications, or an unknown cause. If this occurs, the excess fluid is aspirated.

The laboratory analyzes are frequently performed on serous fluid, namely: Gross appearance, clotting, cell count and white blood cell differential, specific gravity, protein, LDH, glucose, Gram's stains, and cultures (48). Table 6 shows properties of an inflammated serous fluid and a transudate serous fluid (50 and 51). The Table 7 indicates properties of a serous fluid. A build up of serous fluid is called an effusion. Diagnosis and treatment depend on the classification of a cause: transudate or exudate:

Transudates (49) due to: A systemic disorder (For example congestive heart failure); Disruption in the balanced regulation of fluid filtration (formation) and its reabsorption; and a mechanical process.

Exudates (49) due to: Conditions that directly involve the membranes of the particular cavity (Examples of infections, inflammation, and malignancies; and an inflammatory process.

TABLE 7 Physical and chemical properties of human serous fluid (1:334).

Property	Plasma	Transudates	Pleural Fluid	Pericardial Fluid	Peritoneal Fluid
Physical properties					
Conductivity, mho × 1000	(10.5–12.4)	14.2 (11.3–15.5)	—	—	13.4 (13.2–13.5)
pH	7.39 (7.33–7.45)	(7.45–7.68)	7.64 (760–7.68)	—	—
Specific gravity	1.027 (1.025–1.029)	(1.005–1.015)	1.013	—	—
Chemical components					
Ash, %	(0.6–1.0)	—	0.76	0.67	0.98

9.9 HEMARTHROSIS

Recurrent or chronic hemarthrosis is the most common complication of a group of heritable disorders of blood coagulation. Hemarthrosis can be a complication of anticoagulant therapy or severe trauma to a normal joint. In hemophilia, joint bleeding usually begins before the age of five and tends to recur repeatedly during childhood in response to even minor injury. The most common sites are the knees, elbows, and ankles, but any joint can be involved.

Acute hemarthrosis usually results in marked local inflammation and joint symptoms that can last for days to weeks. Approximately one half of patients with hemophilia develop chronic deformities in one or more joints. Some of them develop a chronic progressive synovitis, restricted to one or a few joints, which clinically and roentgenographically resembles rheumatoid arthritis. In chronic cases there is marked synovial membrane hyperplasia, destruction of articular cartilage, and erosions of

subchondral bone. This chronic progressive pattern probably results from a low level of continuous or intermittent bleeding into involved joints. Joint fluid, in chronic cases, usually contains blood and very high levels of leukocyte-derived proteases. Other musculoskeletal manifestations of hemophilia include bleeding into muscle and bone. The resolution of large hematomas can produce chronic cysts within these tissues (29).

Figures 20 to 22 show hemarthrosis in a knee, in the X-ray films. In these Figures, one can observe the blood over the joint (light tone in the film around the bone). The ultrasonogram also shows the internal bleeding in the joint between the femur and the tibia (38).

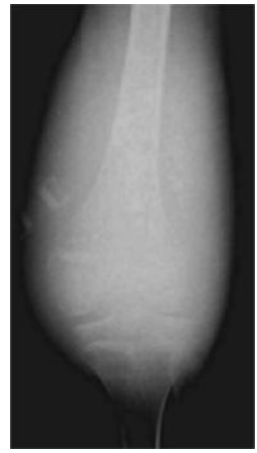

FIGURE 20 AP film of knee with hemarthrosis of the left knee (38).

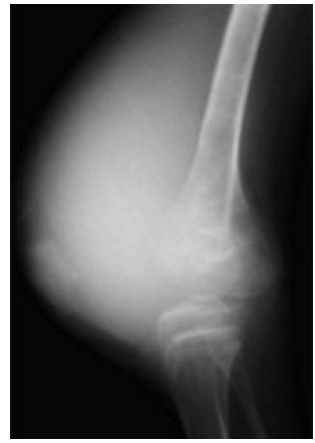

FIGURE 21 Lateral films of left knee (38).

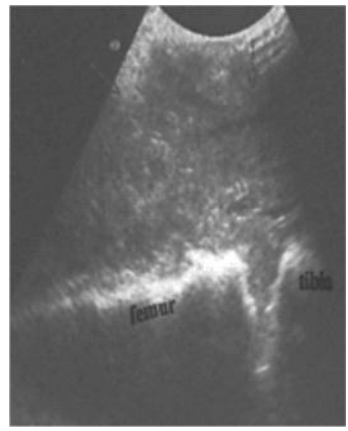

FIGURE 22 An ultrasonogram of his left knee (38).

9.9.1 MANAGEMENT OF HEMARTHROSIS

Acute hemarthrosis should be managed by immobilization, analgesic therapy, and the administration of appropriate plasma concentrates that contain the required coagulation factor. Aspirin and other nonsteroidal analgesics that alter platelet function should be avoided. If there is marked distention of a joint or bursa, aspiration can be accomplished after the defect in coagulation has been corrected. When pain and acute inflammation have subsided, an exercise program to restore range of joint motion should be initiated. For the patient with severe chronic deforming joint disease, the availability of potent plasma concentrates has made it possible to perform synovectomy and arthroplasty in selected instances (29).

9.10 ARTHROCENTESIS

It is a puncturing of a joint space (knee, shoulder, etc.) with a sterile needle to: Withdraw fluid for diagnosis and/or treatment of a condition; and inject medications into the joint space.

9.10.1 REASONS FOR ARTHROCENTESIS (14)

- Diagnose and/or treat a painful, swollen, fluid-filled joint.
- Diagnose the specific type of arthritis occurring within a joint.
- Verify the presence of an infection, identify the causative agent, and follow the progress of antibiotic therapy.
- Check for crystals in the joint fluid, which could be a sign of gout.
- Inject medications into the joint space, such as an anesthetic or an antiinflammatory agent (e.g., cortisone).

9.10.2 PROCEDURE

The doctor will examine the joint and find the best spot to enter the joint. The skin is cleaned with an antiseptic. The doctor will then numb the area, either with a cream or spray, or with an injection using a tiny needle. The aspirating needle is then inserted and guided into the joint space. The person under going the procedure may feel a

"pop" as the needle enters the joint capsule. The excess fluid is drawn up into the syringe and the needle is removed. A bandaid is usually applied. Figure 23 gives us an idea of the procedure for the removal of excess fluid in the joint (45).

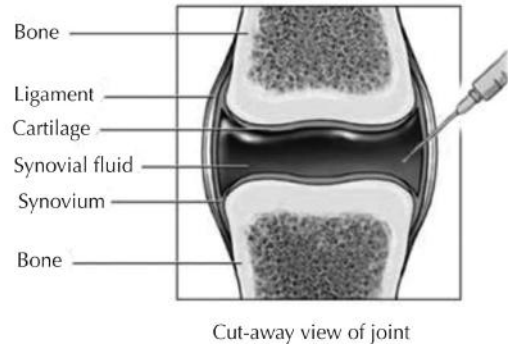

FIGURE 23 Treatment procedure for arthrocentesis (45).

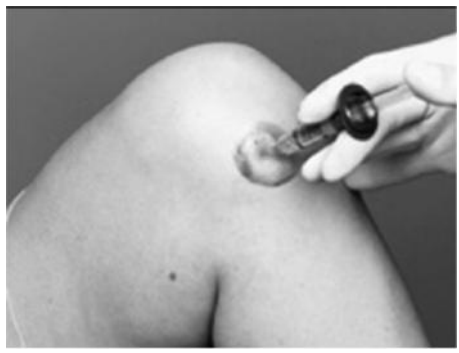

FIGURE 24 Injecting a knee joint

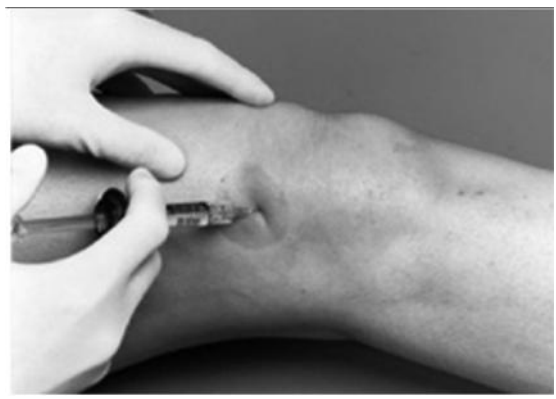

FIGURE 25 Alternative method for injecting a knee joint.

9.10.3 RISK FACTORS FOR COMPLICATIONS DURING THE PROCEDURE (45)

- Infections or abrasions of adjacent skin.
- Preexisting bleeding disorder.
- Use of blood thinners (anticoagulants), with poorly controlled blood levels.
- Allergic reaction to local anesthetic.

9.10.4 OUTCOME (14)

If arthrocentesis is done as a diagnostic test, the laboratory report on the fluid may reveal the reason for the joint inflammation. If arthrocentesis is done to drain accumulated fluid, pain will diminish and more motion will result. However, one may have a recurrence of the joint fluid depending upon the reason for the initial fluid build up. The doctor can carefully monitor the progress. If antiinflammatory medications are injected into the joint, they may help to decrease inflammation and pain within the joint. Over time, these effects will wear off and one may require further treatment.

9.11 TREATMENT OF ARTHRITIS

Many options for treatment of arthritis are available: From overthe-counter medicines, such as aspirin, to prescription medicines, such as COX-2 specific inhibitors, to surgery. Diet and exercise are also an important part of the treatment plan. Alternative therapies, such as dietary supplements and acupuncture, are being used more widely. In this chapter, we will focus on viscosupplementation and COX-2 inhibitors (15).

9.11.1 VISCOSUPPLEMENTATION (15)

The pathologic changes of synovial fluid hyaluronic acid, with its decreased molecular weight and concentration, led to the concept of viscosupplementation. Viscosupplementation came into clinical use in Japan and Italy in 1987; in Canada in 1992; in Europe in 1995; and in the United States in 1997. Two hyaluronic acid products are currently available in the United States: Naturally occurring hyaluronan (Hyalgan) and synthetic hylan G-F 20 (Synvisc). Hylans are cross-linked hyaluronic acids, which gives them a higher molecular weight and increased elastoviscous properties. The higher molecular weight of hylan may make it more efficacious than hyaluronic acid because of its enhanced elastoviscous properties and its longer period of residence in the joint space (i.e., slower resorption). Common side effects of hylan include pain, stiffness, and redness at the site of injection.

The exact mechanism of action of viscosupplementation is unclear. Although restoration of the elastoviscous properties of synovial fluid seems to be the most logical explanation, other mechanisms must exist. The actual period that the injected hyaluronic acid product stays within the joint space is on the order of hours to days, but the time of clinical efficacy is often on the order of months.[4] Other postulated mechanisms to explain the long-lasting effect of viscosupplementation include possible antiinflammatory and antinociceptive properties, or stimulation of in vivo hyaluronic acid synthesis by the exogenously injected hyaluronic acid.

9.11.2 INJECTION TECHNIQUE FOR HYALURONIC ACID (15)

Hyalgan is supplied in 2-ml vials (one injection per vial) or prefilled syringes, and Synvisc is supplied in 2-ml prefilled syringes. The recommended injection schedule is one injection per week for five weeks for Hyalgan, and one injection per week for three weeks for Synvisc. Repeat courses of viscosupplementation can be performed after six months.

A knee joint can be injected several ways. One approach is to have the patient lie supine on the examination table with the knee flexed 90 degrees (Fig. 24). In this position, the anterior portions of the medial and lateral joint lines can easily be palpated as dimples just medial or lateral to the inferior pole of the patella. Often, the medial joint line is easier to palpate and define and can be chosen as the site of injection.

Alternatively, the knee joint can be approached with the knee extended, again with the patient lying supine (Fig. 25). The patient lies supine on the examination table with the right knee extended. The injection site is marked along the superolateral corner of the patella. The needle is angled slightly toward the underside of the patella. The femur is to the left, and the tibia is to the right (15). Most commonly the superolateral edge of the patella is the site of injection, but other quadrants of the knee near the patellar edges can also be chosen. With this approach (knee in extended position), the needle is generally aimed under the patella.

Whichever approach is used, the actual injection site can be marked with a fingernail imprint or the barrel of a pen. Next, sterile preparation with a povidone iodine preparation (Betadine) and alcohol can be performed. A 22- to 25-gauge needle can be used for the injection. Local anesthesia with lidocaine before the injection can be used. Alternatively, an ethyl chloride spray can be used for local anesthesia. Following puncture through the skin and into the joint space, the injection is accomplished. If resistance is encountered, redirection of the needle may be necessary.

If effusion is present, **aspiration of the joint** is recommended before the injection to prevent dilution of the injected hyaluronic acid. The aspiration can be performed at the same site as the injection, as previously described. The same needle can be left in place and used for the aspiration and the injection. In either case, the aspiration may require a larger bore needle, such as an 18- or 20-gauge needle. Following local anesthesia with intradermal lidocaine or ethyl chloride spray, the needle can be placed into the joint for aspiration. When aspiration is completed, hemostat clamps can be used to grasp and stabilize the needle, while the aspiration syringe is detached from the needle. The syringe containing hyaluronic acid can then be attached to the same stabilized needle followed by injection. Alternatively, separate needle sticks can be performed, one for aspiration and another for injection.

No excessive weight-bearing physical activity should take place for one to two days following injection. Otherwise, no specific postinjection instructions are necessary.

9.11.3 COX 2 INHIBITORS (15)

Non-steroidal antiinflammatory drugs (NSAIDs) are often used to relieve pain caused by osteoarthritis. NSAIDS work by inhibiting cyclooxygenase (COX), the enzyme involved in the production of prostaglandins. Prostaglandins contribute to pain and

inflammation, so blocking their production relieves pain. Unfortunately, blocking the production of prostaglandins also depletes the body of "good" prostaglandins that protect the stomach from ulcers, assist with blood clotting and maintain blood flow to the kidneys. It has now been found that there are two types of COX: COX 1 and COX 2. Many of the "bad" prostaglandins that cause pain are made by COX 2, while the "good" prostaglandins are mostly made by COX 1. By blocking only only COX 2 and leaving COX 1 alone, pain can conceivably be relieved without many of the common side effects of NSAIDs.

COX 2 inhibitors are already used in Europe and in the United States. The most common medication used now in the treatment of arthritis is Celebrex. Celebrex blocks the action of the COX-2 enzyme, which plays a key role in pain and inflammation. Celebrex was the first COX-2 specific inhibitor approved for treating the pain, inflammation, and stiffness that accompanies arthritis (both OA and RA). And today, Celebrex treats a broad range of painful conditions, including OA, RA, acute pain, and painful menstrual cramps in adults. Celebrex is generally well tolerated.

9.12 RECENT AND FUTURE INVESTIGATIONS

Arthritis is a theme of great clinical importance due to the fact that it affects both health and quality of life of many persons. Through the years researches have been able to come up with most effective ways to control human body pain and the disorders. Though no single cure has been found for all types of arthritis, yet it has become possible to manage the pain associated with arthritis. In this chapter, we discussed recent investigations on the human body pain and arthritis around the world.

Dr Sally Roberts, Director of spinal research at the Robert Jones and Agnes Hunt Orthopaedic Hospital in Oswestry-UK, was awarded a GB£116 millions three-year grant from the medical research charity to research the role of cell failure in intervertebral discs (20). Intervertebral disc are the small pieces of fibrocartilage in between vertebrae that allow the spine to bend and be flexible. But when they wear away, the bones in the spine rub together, often causing pain. A large proportion of back pain is caused either directly or indirectly by the breakdown or degeneration of intervertebral discs, which is due ultimately to disc cell failure. "Cells of the disc are responsible for producing and maintaining its structure, however cells in the disc are few and far between and are often found to be unhealthy, particularly when people develop certain disc diseases, " explains Dr Roberts. Cells in the body can die in different ways: it can happen in a controlled and planned way (apoptosis) which does little damage to the cell's surroundings, or it can be totally uncontrolled (necrosis) where the cell breaks open traumatically, usually causing damage to the surrounding tissue. Dr Roberts plans to study how cells die in the disc, as little is known of this. "We plan to investigate how these cells die in human discs with different diseases, and also study living disc cells in the laboratory to identify what factors make them die, and in what way." she added. "This should help us understand how cell death happens in disc cells, and whether the process can be reversed, which would have a major impact on the millions of people who suffer from chronic back pain."

Dr Ian Clark, Reader in Cell Biology at the University of East Anglia, was awarded a GB£78,088 grant for 18 month by the Arthritis Research Campaign to track down an

enzyme that might break down the tissue of the body, including cartilage in the joint. «We have discovered that a new enzyme called ADAMTS-16 that is found in very high levels in the cartilage of patients with osteoarthritis. These enzymes break down tissues of the body such as cartilage, and can be viewed as biological scissors, which chop up the components making up these tissues. Usually the body controls these enzymes very carefully; however, in arthritis this control is lost and the joint is damaged," comments Dr Clark. His reserach aims to find out exactly the function of this enzyme in cartilage. According to his hypothesis, if it is responsible for cartilage damage, it can lead to the development of new types of treatments to counter these effects.

The Arthritis Research Campaign (ARC) is the fourth biggest medical research charity in the United Kingdom and the only one solely dedicated to finding the cause and cure of all kinds of arthritis. Norwich is a leading center of funded research by ARC.

A team of Manchester researchers are hopeful that their research into arthritic pain could lead to new painkilling drugs within the next five years (19).

The researchers at Hope Hospital believe the new drugs will work on the part of the brain that controls chronic pain, and may signal a major breakthrough in the treatment of chronic pain syndromes such as osteoarthritis, and fibromyalgia. At the Human Pain Research Laboratory at the University of Manchester's Rheumatic Disease Centre at Hope Hospital in Salford, the team, led by Dr Anthony Jones, has identified abnormal brain mechanisms in people with fibromyalgia: a common, but poorly understood chronic pain syndrome affecting the muscles.

Working with colleagues at Université René De Carte in Paris, the scientists now hope to develop a drug compound that has the potential to boost natural opiates in the brain called endorphins. Patients with OA and fibromyalgia from the North- and healthy volunteers have been taking part in a five year £800,000 program funded by the ARC, to study how different parts of the brain deal with different types of pain. Preliminary results show that chronic pain suffered by osteoarthritis and fibromyalgia patients is controlled by a completely different part of the brain. Using brain scanning and imaging techniques, the team established that when they inflicted sharp pain on healthy volunteers, pain was activated more by the lateral part of the brain – the part that indicates the location of a pain. However, the kind of on-gong pain suffered by people with osteoarthritis was dealt with more by the medial side of the brain – the part that is more connected to emotions. "We now know that there is a completely different set of chemicals involved in controlling the medial and lateral pain systems in the brain. One of the sets of chemicals are natural pain killers called endorphins, which are found in high concentrations in the medial pain system, and which can be enhanced naturally by, for example, taking exercise," indicates Dr Jones.

Further tests to measure the brain activity of people with fibromyalgia showed that when a sharp pain was applied to the arm, they were unable to switch processing the unpleasantness of the pain in the medial system when asked to think about the location of the pain, rather than the unpleasantness; thus revealing an abnormal mechanism in their brain. Healthy pain-free volunteers had no problem switching processing between the two pain systems. "People with fibromyalgia were unable to shift their attention from the emotional side of the pain, demonstrating that there is an abnormal

mechanism in their brains," explains Dr Jones. "We think people with fibromyalgia may have a chemical difference in the brain compared to healthy people, and that it is not a problem with the muscles. They have an inability to mobilize the endogenous opiate system, which we think could be helped by new drugs. We are very excited about these preliminary results of our work and its potential clinical impact, because apart from paracetamol, and the more widespread use of antidepressants for chronic pain, there have not been any major developments of new classes of painkilling drugs for arthritic pain since the last century."

People with early stage rheumatoid arthritis should receive aggressive care (19), including monthly outpatient assessments and escalated therapy based on disease activity, in order to achieve better outcomes, according to research presented at the American College of Rheumatology Annual Scientific Meeting in Orlando, Florida.

A cohort of 110 patients with active rheumatoid arthritis who had the disease for less than five years were randomized to receive routine outpatient care or intensive outpatient care, and followed for 18 months. Routine outpatient care was delivered in the rheumatology clinics of two hospitals in Glasgow – Scotland. Intensive care consisted of monthly outpatient assessments with careful measurement of the activity of the arthritis, joint injections of corticosteroids, and the targeting of persistent disease activity using a protocol to escalate disease-modifying antirheumatic drug (DMARD), therapy including methotrexate, cyclosporine, and sulfasalazine, in patients with persistent disease activity. Results showed that 67% of patients in the intensive care group achieved very marked improvement in the arthritis at 18 months as measured by standard criteria of disease activity developed by the American College of Rheumatology (ACR 20, 50, 70), compared to 18% of patients in the routine outpatient care group. In addition, patients in the intensive outpatient care group demonstrated improved physical function and quality of life, and had less joint damage as assessed by radiographs.

"Rheumatoid arthritis is a severe disease that results in pain, disability and a reduction in quality of life," said Duncan R. Porter, MD, Consultant Rheumatologist and researcher at Gartnavel General Hospital, Glasgow – United Kingdom. "His study shows that patients need to be treated intensively, and that persistent disease activity must be targeted by escalating therapy in an attempt to control the disease in the early years. If this is done, then the symptoms, physical function and quality of life improve very substantially."

The roots of Thunder God Vine, a plant whose leaves and flowers are highly toxic, have been used medicinally in China for over 400 years (32). A root extract of this plant has been shown to safely and effectively reduce pain and inflammation in a small group of people with treatment-resistant RA, according to a study funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The randomized, double blind, placebo-controlled trial, published in the July issue of Arthritis and Rheumatism, is the first to test the use of an extract of this vine in rheumatoid arthritis patients in the United States.

Twenty-one rheumatoid arthritis patients completed a 20-week clinical trial of the ethanol/ethyl acetate extract. Patients were randomly assigned to one of three treatment groups: placebo, low-dose extract, or high-dose extract. After four weeks, 80 percent of patients in the high-dose group and 40 percent in the low-dose group showed rapid

improvement in symptoms compared with no improvement in the placebo group. Side effects were minor for all three-treatment groups. Long-term studies with larger numbers of patients are needed to confirm the safety and benefits of the treatment. According to senior author Peter Lipsky, M.D., scientific director of NIAMS, the extract is a particularly promizing treatment for RA. It is unique, because it slows down the overactive immune system, reduces inflammation by turning off inflammatory genes such as tumor necrosis factor alpha, and reduces the activity of B and T cells. Dr. Lipsky believes that this plant extract has the potential to treat other immune diseases such as lupus, and is planning to conduct in-depth studies. The extraction process, although time-consuming, is critical because it transforms the otherwise toxic and deadly Thunder God Vine into a therapeutic treatment.

Long-term systemic, or widespread, inflammation experienced by patients with RA leads to an increased risk of death from cardiovascular disease, according to research presented at the American College of Rheumatology Annual Scientific Meeting in Orlando, Florida (32). The relationship between inflammation from rheumatic disease and cardiovascular disease is an emerging field of study, and this research offers another indication that these are linked. The study used data resources from the Rochester Epidemiology Project in Minnesota to identify a group of 603 adult patients with RA, followed for approximately 40 years from the time they were diagnosed. Researchers estimated the influence of 13 traditional heart disease risk factors such as weight, cigarette and alcohol use, diabetes and high blood pressure, and for eight rheumatoid arthritis disease characteristics. The study revealed that, independent of the common risk cardiovascular disease factors, several key characteristics of severe RA stood out as being associated with markedly higher risk of death from cardiovascular disease: high erythrocyte sedimentation rate and large-joint swelling at incidence, rheumatoid arthritis complications including RA related vasculitis or lung disease, and destructive changes on X-ray of the joints.

According to the American Heart Association, cardiovascular disease is the leading cause of death among adults in the United States, affecting one in five adults and causing nearly 1 million deaths annually. Patients with RA are twice as likely to develop serious cardiovascular disease.

"An important goal of our research is to raise awareness of the risks of cardiovascular disease among people with rheumatoid arthritis," said Sherine Gabriel, MD, professor of Medicine and Epidemiology at the Mayo Clinic in Rochester – Minnesota and the senior investigator in the study. "The characterization of the risk factors for cardiovascular disease will help us to identify those patients with rheumatoid arthritis at highest risk in order to better target our preventive strategies."

Baseline results of the blood test for C-reactive protein are a good predictor of the risk of death from heart disease in patients with inflammatory polyarthritis, indicating a direct link between C-reactive protein and cardiovascular disease, according to research presented at the American College of Rheumatology annual meeting in Orlando, Florida (32). C-reactive protein is released by the body in response to acute injury, infection, or other inflammatory triggers; and is recognized as an agent in cardiovascular disease and in arterial inflammation. It is often present in elevated levels in patients with RA and inflammatory polyarthritis. In this study, 506 patients with

inflammatory polyarthritis newly diagnosed between 1990–1992 were recruited from the Norfolk Arthritis Register in the United Kingdom, a database of patients with inflammatory polyarthritis including RA. Patients were followed for mortality notification and follow-up over ten years, to 2001. Blood samples from the participants were analyzed for rheumatoid factor (RF) and C-reactive protein concentration to determine baseline levels at the start of the study. During the period studied, 38% of reported deaths were due to cardiovascular disease. Patients whose blood showed elevated C-reactive protein concentrations were about four times as likely to be at risk of death from heart disease, regardless of gender, age, or other risk factors including smoking. Those who were RF positive were at an increased risk, as well.

"Cardiovascular disease is rapidly becoming one of the most important long-term complications of rheumatoid arthritis," said Dr. Alan Silman, Director of the United Kingdom's Arthritis Research Campaign Epidemiology Unit at the University of Manchester Medical School, and professor of Rheumatic Diseases Epidemiology at Manchester University in England, and an investigator in the study. "This research helps in identifying those patients who might be most at risk so that appropriate intervention and preventive strategies might be employed."

Researchers at the Mayo Clinic funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have identified markers that are early indicators of progressive disease in RA. Jörg Goronzy, M.D., and his colleagues found that the following factors present at disease onset predict X-ray evidence of fast progression (32):

- Older age.
- Bone that has worn away (erosions).
- Rheumatoid factor, an antibody in the blood.
- Rheumatoid factor titer (measurement of amount of rheumatoid factor in reaction with a specific testing medium).
- Variations in specific genes related to immune function and to the protein uterglobin.
- T cells (CD4+, CD28null) associated with an aging immune system.

The research looked at many possible biologic markers for their predictive potential, and ruled out some potential markers, including initial joint pain and swelling.

The two-year study followed the disease progression of 111 patients with recent diagnoses of RA. Each participant received the same baseline treatment, one that was stepped up only when joint inflammation did not significantly improve. About half of the patients never developed erosive disease. These findings suggest that more appropriate treatment strategies could be based on likely disease course, and underscore the need for further investigation.

RA is a form of arthritis that causes inflammation of the joint lining and often affects many different joints. It can damage the cartilage, bone, tendons and ligaments, causing pain, stiffness, swelling and loss of joint function. RA progression can vary widely, and early aggressive treatment with disease-modifying antirheumatic drugs is frequently recommended, although there are some toxicity risks.

9.13 CONCLUSIONS

Body pain and arthritis disorders are of high clinical importance because of the great impact on the quality of life for the individuals affected by these conditions. The pathophysiologic mechanisms that underlie the development of most forms of arthritis and connective tissue disorders are still obscure and treatment is still not specific in many cases, because it is not known if they are congenital disorders or bacterial induced specifically. The latest form of treatments includes viscosupplementation and COX 2 inhibitors. In viscosupplementation treatment, the liquid is inserted as a substitute for the synovial fluid and COX 2 inhibitor pills is an option. Current research focuses to clarify etiologic mechanisms and to develop more therapies. Many of the connective tissue disorders affect not only the bones or joints but also the muscles and skin. Musculoskeletal disorders, like arthritis, may represent localized trauma, inflammation, or congenital defects. Most joints in the body are diarthroses, in which articulating bones are covered with weight-distributing cartilage and connected by ligaments that allow movement within the range of motion. A capsule encloses the joint, and a vascular, innervated synovial membrane lines the capsule. Synovial fluid, secreted by the synovial membrane, lubricates and nourishes joint structures. Traumatic and inflammatory conditions affecting diarthrotic joints may result in damage to cartilage, ligaments, and bones within the joint. The arthritis disease affects people of all ages and both sexes.

9.14 SUMMARY

The word “arthritis” literally means joint inflammation (“arthr-” means joint; “-itis” means inflammation). It refers to more than 100 different diseases that affect the area in or around joints, such as muscles and tendons. Some of these diseases can also affect other parts of the body, including the skin and internal organs. Arthritis usually causes stiffness, pain and fatigue. Over 43 million Americans have arthritis, according to the Arthritis Foundation. It affects people of all ages, but it is common in older persons. This chapter focuses on the synovial fluid and the articular cartilage. The synovial fluid is a fluid that resides in the human body joint to lubricate the joint. The articular cartilage is located in the synovial joints of the human body and plays the important role to increase the area of load distribution and to provide a smooth wear resistant surface. One of the most common forms of diagnosing arthritis is by arthrocentesis: Procedure in which the joint space is punctured with a sterile needle to withdraw fluid, in this case, the synovial fluid. Arthrocentesis also refers to the procedure of injecting medications into the joint space. Many treatment options are available for arthritis: from overthe-counter medicines, such as aspirin; to prescription medicines, such as COX-2 specific inhibitors; to surgery. Diet and exercise are also an important part of the treatment plan. Alternative therapies, such as dietary supplements and acupuncture, are being used more widely. This chapter focuses only on viscosupplementation and COX-2 specific inhibitors.

KEYWORDS

- **Aetiology**
- **Anesthetic**
- **Antibiotic**
- **Anti-coagulant**
- **Anti-inflammatory**
- **Anti-rheumatic**
- **Arthritis**
- **Arthrocentesis**
- **Arthroplasty**
- **Autoimmune disease**
- **Bursa**
- **Bursitis**
- **Calcification**
- **Cartilage**
- **Coagulation**
- **Collagen**
- **Corticosteroids**
- **COX-2 inhibitors**
- **Crystal deposition**
- **Diarthrodial joint**
- **Dislocation**
- **Electrolytes**
- **Endorphins**
- **Enzyme**
- **Extracellular matrix**
- **Fibrocartilage**
- **Fibromyalgia**
- **Germ**
- **Glycoproteins**
- **Gout Hemarthrosismatomas**
- **Hyaline cartilage**
- **Hypertrophy**
- **Idiopathic**
- **Immune system**
- **Infectious arthritis**
- **Inflammation**
- **Intrasynovial**

- **Joint**
- **Larynx**
- **Ligaments**
- **Lubrication**
- **Membrane**
- **Nodule**
- **Non-steroidal**
- **Olecranon bursitis**
- **Osteoarthritis**
- **Paracetamol**
- **Pathology**
- **Permeability**
- **Plasma**
- **Polyarthritis**
- **Prostaglandins**
- **Proteoglycans**
- **Psoriasis**
- **Psoriatic arthritis**
- **Rheumatic disorder**
- **Rheumatology**
- **Scintigraphy**
- **Sclerosis**
- **Rheumatic disorder**
- **Serous fluid**
- **Swelling**
- **Synovectomy**
- **Synovial fluid**
- **Synovial membrane**
- **Synovitis**
- **Tendon**
- **Toxic synovitis**
- **Ultrasound**
- **Vasculitis**
- **Viscoelastic material**
- **Viscosuplementation**

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APPENDIX I: NUMERICAL EXERCISES

1. How much pressure does the knee of a 175-pound person bears if the articular cartilage measures 9 cm diameter?
   $A = \pi \times [(0.009 \text{ m}) / 2]^2 = 0.0063617 \text{ m}^2$
   $F = W = 175 \text{ lb} \times [4.44822 \text{ N} / 1 \text{ lb}] = 778.439 \text{ N}$
   $F_{knee} = 778.439 \text{ N} / 2 = 389.219 \text{ N}$ for each knee
   $\sigma = F_{knee}/A = 389.219 \text{ N} / 0.0063617 \text{ m}^2 = 6118.4 [\text{N/m}^2 \times (\text{Pa}/ \text{N/m}^2)] = 6120$ Pa or 6.12 kPa for each knee
2. If the specific gravity of a synovial fluid is 2.388 and the density of water is 1000 kg/m^3, determine the density and the specific weight of the synovial fluid.

Density = 2.388 × 1000 kg/m^3 = 2,388 kg/m^3
Specific weight = 2.388 × 9810 N/m^3 = 23,426.3 N/m^3

3. Determine the specific volume of a synovial fluid if its specific weight is 24,500 N/m^3.
Specific weight = $\gamma = \rho\, g = [g / v_s]$ or
$v_s = [g / \gamma] = [9.81 m/s^2 / 24{,}500 N/m^3] = 400.408 \times 10^{-6}$ m^3/kg

APPENDIX II: LUBRICATION FORCES DUE TO A THIN FILM BETWEEN TWO SURFACES (47)

We shall consider the case of a lubrication layer between two flat surfaces, one of which is inclined and moves relative to the other. In this case,

$$h(x) = h_1 - \frac{h_1 - h_2}{L} x \tag{8}$$

This exercise demonstrates remarkably high normal forces that can be generated in lubrication layers and the very low relative friction that occurs in the longitudinal direction. The flow geometry is that of a slider bearing in machine design. An obvious physiological reference is the lubrication of diarthrodial joints within the body. Such biological lubrication is a biomechanically sophisticated and complex phenomenon. The lubricating fluid is synovial fluid, which contains a small cellular component and hylauronic acid, a long-chain polymer that is found at many places within the body. The lubrication mechanism in diarthrodial joints depend not simply upon the properties of synovial fluid, but also upon the roles of the adjacent cartilage and other mechanisms. Our model lubrication problem here focuses exclusively upon viscous lubrication effects by a thin film of fluid. Here, we consider a Newtonian fluid. Exact analytic solutions for nonNewtonian fluids in lubrication problems are rare. Nonetheless, this example demonstrates how movements of opposing surfaces in our diarthrodial joints can support forces much higher than, for example, our body weights.

In this exercise, the pressure is obtained by combining Eq. (8) with the Reynold's Eq. (6) and integrating for the boundary condition, p (x) = P_A at hr = h_2.

$$p(x) - p_A = \frac{6\mu U}{\alpha(h_1 + h_2)} \left[\frac{(h_2 - h)(h - h_1)}{h^2} \right] \tag{9}$$

Where:

$$\alpha = \frac{h_1 - h_2}{L} \tag{10}$$

The vertical force or load F_N acting on the upper surface is obtained by resolving the pressure stress into the vertical direction and integrating along the length L. The depth of the surface in the z-direction is W. The integration is facilitated by changing the variable of integration from x to h:

$$F_N = \frac{-W}{(1+\alpha^2)^{\frac{1}{2}}}\int_0^L (p - p_A)\,dx$$

$$= \frac{W}{\alpha(1+\alpha^2)^{\frac{1}{2}}}\int_{h_1}^{h_2}(p - p_A)\,dh = \frac{1}{(1+\alpha^2)^{\frac{1}{2}}}\left(\frac{6\mu UW}{\alpha^2}\right)\left(\ln\beta - 2\frac{\beta-1}{\beta+1}\right) \qquad (11)$$

Where: $\beta = h_2/h_1$. Quite often, $\alpha << 1$. Therefore for algebraic simplicity, we shall neglect the factor $(1+\alpha)^{-1/2}$ for rest of the analysis. The tangential force F_F acting on the upper, sliding surface has two components. One, F_V is obtained by integrating the viscous stress $\tau_{yx}(x, h)$ along the length of that surface:

$$\tau_{yx}(x,h) = \mu\frac{dv_x(x,h)}{dy} = \frac{\mu U}{h} + \frac{h}{2}\frac{dp}{dx} = \frac{\mu U}{h} + \frac{4h}{2}\frac{dp}{dx}$$

$$= 2\mu U\left(\frac{3h_1h_2}{h_1+h_2}\frac{1}{h^2} - \frac{1}{h}\right) \qquad (12)$$

$$F_V = W\int_0^L \tau_{yx}dx = -W\frac{1}{\alpha}\int_{h_1}^{h_2}\tau_{yx}dh = \frac{2\mu U}{\alpha}W\left(3\frac{\beta-1}{\beta+1} - \ln\beta\right) \qquad (13)$$

Strictly speaking, there is a component of the pressure in the *x*-direction that contributes a force F_p to F_F. The force, F_p, is given below:

$$F_p = \frac{W_\alpha}{(1+\alpha^2)^{\frac{1}{2}}}\int_0^L (p - p_A)\,dx \qquad (14)$$

$$F_p = \frac{W}{(1+\alpha^2)^{\frac{1}{2}}}\int_{h_1}^{h_2}(p - p_A)\,dh \qquad (15)$$

Since $\alpha^2 << 1$, Eq. (15) reduces to:

$$F_p = W\int_{h_1}^{h_2}(p - p_A)\,dh = \left(\frac{6\mu UW}{\alpha}\right)\left(\ln\beta - 2\frac{\beta-1}{\beta+1}\right) \qquad (16)$$

The resultant force is a sum of two components: Hotizontal and vertical.

$$F_F = F_V + F_p, \qquad (17)$$

Therefore summing Eqs. (13) and (16), and simplifying, we get:

$$F_F = \left(\frac{2\mu UW}{\alpha}\right)\left(2\ln\beta - 3\frac{\beta-1}{\beta+1}\right) \qquad (18)$$

The ratio of the tangential to the normal force is shown below:

$$\Re = \left(\frac{\alpha}{3}\right)\left[\frac{2(\beta+1)\ln\beta - 3(\beta-1)}{(\beta+1)\ln\beta - 2(\beta-1)}\right] \tag{19}$$

As a numerical exercise, consider a layer of dimensions h_1=1.2 mm, h_2=1 mm, and L=5 cm. The ratio $\Re$ = 0.07, a very low frictional effect.

CHAPTER 10

BIOMECHANICS OF ORTHOPAEDIC FIXATIONS[1, 2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Xiomara Bracero, Jackxander Perez, Yarielaine Rodriguez, Rebeca Ruiz, Carmen Altieri, Juan Flores, Vladillen Gonzalez and Angel Rodríguez) for the course on Mechanics of Materials – I, INGE 4011. Course Instructor: Megh R. Goyal, PhD, PE Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com> or visit at: <http://www.ece.uprm.edu/~m_goyal/home.htm>. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez; and Dr. Alberto Ramos, Orthopaedic Surgeon at Puerto Rico San Pablo Hospital, Bayamon.

[2]The numbers in parentheses refer to cited references in the bibliography.

10.1 INTRODUCTION

Biomaterials improve the quality of life for an ever-increasing number of patients each year. The range of applications includes joint and limb replacements, artificial arterie, skin, contact lenses, and dentures, etc. The implementation of biomaterials may be for medical reasons such as the replacement of diseased tissues required to extend life expectancies. Other reasons may include purely esthetic ones including breast implants. This increasing demand arises from an aging population with higher quality of life expectations. The biomaterials community is producing new and improved implant materials and techniques to meet this demand, but also to aid the treatment of younger patients where the necessary properties are even more demanding. A counter force to this technological push is the increasing level of regulation and the threat of litigation. To meet these conflicting needs, it is necessary to have reliable methods of characterization of biomaterial and material/host tissue interactions. Due to increasing demand and advanced technology, new biomaterials are being developed such as: Titanium, Stainless steel, Zirconium and Cobalt chrome, etc. In this chapter, we will discuss biomechanics of orthopedic fixations and biocompatible materials for these fixations.

10.2 THE CHARACTERISTICS OF ORTHOPAEDIC ALLOYS

The total hip prosthesis is not made from pure metals, but from orthopedic metal alloys, specially produced for fabrication of artificial joints. The demand on the orthopedic alloys is increasing level of regulation. The alloy must be: **Very strong** – it must not break or even bend permanently under heavy loads; **Not too stiff** – a too stiff device will "stress shield" the skeleton too much; and **Biocompatible** – must be well tolerated by the bone tissue.

10.2.1 HOT ISOSTATIC PRESSING

All metal alloys for manufacture of orthopedic implants are solidified solutions of crystals. All, at some stage, are melted and allowed to cool in a mold. During cooling process, the metal alloy crystallizes and contracts. The crystals are known as grains and may vary greatly in size.

Very large grains, as in cast cobalt chrome alloy, can lead to catastrophic failure of implants. During cooling process, material shrinks, thus creating voids in the structure of the cold alloy. For optimum mechanical properties of the metallic orthopedic device: the crystal size in the alloy must be uniform, the structure must be free of voids, and the alloy should not contain any impurities. It is impossible to have 100% perfect material suitable for implants. Therefore, the manufacturers use mechanical working of the cast alloys to close the voids between individual crystals and to expel the impurities. One such method is called **Hot Isostatic Pressing** (HIP or "hiping") of cast materials. In HIP, the components are subject to high pressure of at least 1000 atmospheres at temperatures of at least 1100° C, but below the melting point of the alloy, in an oxygen free atmosphere, such as argon.

The hiping is particularly suitable to improve mechanical properties of cast cobalt-chrome components. The process produces plastic flow of the alloy thereby collapsing voids and cavities in the material that might have acted as initiators of device fracture.

Hiped alloy is stronger than «as cast» alloy, but hiping also changes the microstructure of the alloy. The carbides present in the solid solution of the alloy are driven out of the finished product. This process may drastically change some important characteristics of the product, such **as wear resistance.**

10.2.2 CORROSION RESISTANCE

Metallic surfaces in contact with biofluids corrode. The surface dissolves and the dissolved particles of metal enter the circulation. The concentration of the metals (Cobalt, Chromium, or Titan) in the blood increases. The orthopedic alloys are very resistant to this corrosion. Yet, the corrosion occurs when:

- Two dissimilar metals are in contact: This happens in modular total hip stems, at the junction of the ball component with the taper of the shaft component. When both the ball and the stem are made from Cobalt – Chrome alloy, slight corrosion is observed in about 6% of the components. When the ball is from Cobalt-Chrome and the stem is from Titanium alloy, the corrosion is observed in 33% of the components.
- In metal-on-metal total hip joints: There might be wear of the joint surfaces, with production of many small particles of metal alloys. These small particles dissolve in the body fluids.

As a result of these processes, the concentrations of Titanium, Chromium, and Cobalt in the blood and urine for these prostheses are elevated. The trace-metals Cobalt and the Chromium are a part of body's enzyme system, but these metals have caused cancer in workers exposed to large concentrations of these metals. However, there is no proof that elevated serum levels of Cobalt, Chrome, and Titanium produce pathological changes or incite cancer in patients with these total hip prostheses. Blood levels of Aluminum, a metal that is a part of the Titanium alloys, are not elevated in patients with total hip prostheses manufactured from Titanium alloys. The question of the long-term effects of orthopedic metals (Cobalt, Chromium, and Titan) on patients with total hip replacement (THR) is still not concluded. Chromium and Cobalt are excreted by kidneys; in patients with impaired renal function and corroding total hip prosthesis, the blood concentrations of these metals are very high (Brodner). Thus, patients with impaired renal function should have total hip prostheses that do not produce elevated levels of these metals in the blood of these patients. Corrosion resistant orthopedic steel alloys and other orthopedic metal alloys are not ferro-magnetic. Thus, patients with these prostheses can be examined with MRI.

TABLE 1 Mechanical properties of biomaterials.

Material	Young's Modulus	Ultimate Strength	K_{1C}	G_{1C}	Density
Units	GPa	MPa	$MN\text{-}m^{-3/2}$	$J\text{-}m^{2}$	g/cm^{3}
Cortical Bone	7–25	100–150	2–12	600–5000	~2.0
Co – Cr – Mo	230	430–1028	~100	$5x10^{4}$	~8.5

TABLE 1 *(Continued)*

Material	Young's Modulus	Ultimate Strength	K_{IC}	G_{IC}	Density
SS 316L	210	230–1160	~100	—	~8.0
Ti – 6Al – 4 V	106	780–1050	~80	–	~4.5
Alumina	365	6–55	~3	—	–
HA	80	40–200	< 1	—	–
PMMA	3.5	70	1.5	—	–
PE	1	30		—	—
Zirconia	–	—	–	—	6.10
Titanium	–	–	–	–	4.40

TABLE 2 Mechanical properties of Titanium.

Property	Units	Value
Density	Lb/in^3	0.179
	g/cm^3	(4.95)
Metallurgical condition	°F	1.475
anneal		
Tensile	ksi	115
strength	(MPa)	(793)
0.2% Yield strength	ksi	95
	(MPa)	(655)
Elongation	%	22
Reduction in	%	60
area		
Typical	HRC	24
hardness		
Modulus of elasticity	Ksi	17500
Poisson ratio	—	0.33

The implants for orthopedic fixation are based on the LactoSorb® copolymer technology. LactoSorb copolymer is now used in Biomet's orthopedic pins and screws, ACL interference screws, suture anchors, pop rivets, meniscal staples, craniomaxillofacial plates, screws, and panels, and other products. Warren, RI based SwimEx, provides an aquatic alternative to land-based therapy. In this therapy, athletes can run, swim or complete a prescribed therapeutic exercise program against the current for musculosketal problems ranging from sore shoulders to sprained ankles to postoperative

knees. Other alternative to improve the stability of the patient is a computerized knee machine. Table 1 shows properties of biomaterials for orthopedic fixations.

10.2.3 TITANIUM

Titanium is a material with high strength, low weight and outstanding corrosion resistance. For these characteristics, more than 1000 tones of titanium devices are implanted in patients every year. Light, strong and totally biocompatible, titanium is one of few materials that naturally match the requirements for the implantation in the human body. The selection of titanium for implantation is to determinate the most favorable characteristics including low modulus, density and highly damage tolerant. The wheat ratio for titanium and its alloys are: 1.4–1.7 (1.1 is a minimum for an acceptable implant material). Fracture toughness of all high implant alloys is above 50 MPa-1/2 with critical cracks lengths well above the minimum for detection by standard methods of nondestructive testing. A metal's lightness is a positive aid to reducing any fatigue of the surgeon. Titanium in non magnetic, and there is therefore no threat of damage to small and sensitive implanted electronic devices. The density of titanium at 4.51 g-cm^{-3} is midway between that of the light alloys based on aluminum and magnesium and that of steels and nickel alloys. Alloys now available offer tensile strength of around 1400 MPa which compare with many structural steels. Another characteristic is the corrosion resistance in a wide range of natural and chemical environments particularly in respect of the pitting and stress corrosion cracking: Hip and knee prostheses, partial replacements for the long bones, bone fracture plates and screws, plates for cranial surgery and dental implant. Pure titanium is ductile (15 to 25% elongation), and it has an ultimate tensile strength of (approximately 30 ksi (207 Mpa) at room temperature). Titanium and its alloys are about 40% lighter than steel and 60% heavier than aluminum. The combination of moderate weight and high strengths, up to 200,000 psi, gives titanium alloys the highest strength -to-weight ratio of any structural metal roughly 30% greater than aluminum or steel. High purity of titanium metal has yield strength of 35,000 psi with elongation of 55%. The minimum yield strength is 70 ksi with minimum elongation of 15%. The tensile strength may be up to 105 ksi. The specific gravity is 4.54. It is paramagnetic and has low electric conductivity. Mechanical properties of Titanium are shown in Table 2.

10.2.3.1 USES OF TITANIUM

Titanium is used in surgical appliances, and in therapy of skin disorders. It is used as an implant material in orthopedics, oral surgery and neurosurgery. Titanium alloys are used in situations where lightweight strength and ability to withstand temperature extremes are required. It is also used in surgery equipments and wheelchairs. It is used for artificial hips and joints. The physiological inertness of titanium makes it available as a replacement for bones and cartilage in variety surgeries.

10.2.3.2 TITANIUM: HEALTH AND SAFETY ISSUES

Titanium is nontoxic and does not require serious limitations on its use because of health hazards. It is pyrophoric because of its heat-producing reaction with oxidizing elements such as oxygen.

10.2.3.3 BIOCOMPATIBILITY OF TITANIUM AND TITANIUM ALLOYS

Titanium and titanium alloys have been used in biomedical engineering for many years. The applications are varied and include the following: joint replacement parts for hip, knee, shoulder, spine, elbow and wrist, bone fixation materials such as nails, screws, nuts and plates, dental implants and parts for orthodontic surgery and dental prosthetics, heart pacemaker housings and artificial heart valves, surgical instruments for heart and eye surgery, components in high-speed blood centrifuges.

10.2.3.4 TITANIUM VERSUS STAINLESS STEEL

Medical grade titanium alloys have significantly higher strength to weight ratio than the competing stainless steel. The three most common frame materials (stainless steel, aluminum, and titanium) actually have similar modulus.

10.2.4 COBALT – CHROME ALLOYS

Cobalt-chrome alloys are referred to as precious-metal-free alloys. The first cobalt-chrome alloy that was introduced in dentistry in the 1930s was an alloy used in medical implant. It was used in the partial denture technique. In dental usage the term "steel" became a synonym with partial denture alloys consisting of cobalt-chrome alloys. However, this designation is misleading since steel refers to iron alloys containing carbon. The frequently used designation "chrome-cobalt alloy" is also incorrect because by definition this would involve alloys on a chromium base. Besides being used as partial denture alloys, cobalt-chrome alloys such as Wirobond®C (BEGO) has been used as crown and bridge alloys for ceramic veneering. The acrylic veneering of cobalt-chrome alloys generally displays more favorable bond values than with precious-metal alloys. Precious alloys have a negative reputation among some dentists and dental technicians, due to poor process ability, inadequate chemical and biological properties. This prefrence goes so far that consideration is only given to alloys with a high gold content, whose properties are applied to other precious-metal alloys (on palladium or silver base and to alloys with reduced gold content) without reflection.

10.2.4.1 BIOCOMPATIBILITY OF COBALT CHROME

Systemic-toxic reactions can be ruled out due to the low corrosion rates and because of the fact that the released ions are essential elements and such reactions are not described in dental literature. In principle, 100% biocompatibility is not possible for any alloy or very generally for any dental material. The residual risk for Wirobond®C, however, is assessed as extremely minimal.

Dental technicians not only come into contact with the alloy in solid form as cast pieces or finished restoration. During casting and grinding, they also come into contact with smoke and dust, which then enter into the lungs. In the steel industry, it is known that health problems may result through nickel, cobalt and chromium. Howver, care must be taken when processing precious-metal alloys (and all other dental materials) so that least amount of the grinding dust is inhaled. It is important to consider the type and size of particles, the chemical states (ions, dust, —) and the place of resorption.

10.2.4.2 CORROSION OF COBALT CHROME ALLOY

It has been shown that cobalt-chrome alloys display an ion release that is somewhat higher than that of gold alloys, but is still on the same order of magnitude. It is known that the corrosion characteristics of dental alloys are influenced by dental processing, such as casting (2), grinding (8, 9) or ceramic veneering (1, 11, 14). In the case of cobalt-chrome alloys, these effects are relatively small. Ground surfaces were compared with Wirobond®C. By grinding with grain size 1200 selenium carbide paper, the surface was removed only on a "dental order of magnitude," i.e., up to metallic gloss, and not 100 μm as stated in the instructions for the corrosion test. The lower degree of material removal results in values that tend to be higher, but are more realistic in view of daily dental practice. It has been shown that Wirobond®C does not display lower ion release due to boiling in hot water or evaporation. Consequently, the surface has been passivated adequately.

There are many causes that contribute to the corrosion of metals when placed inside the human body. After surgery the pH surrounding the implant is reduced to a pH between 5.3–5.6 typically due to the trauma of surgery. Infectious microorganisms and crevices formed between components can reduce oxygen concentration. Both of these factors contribute to the corrosion of the implant.

Materials used must meet the biocompatibility constraints set forth by the Food and Drug Administration (FDA). If a company wants to introduce a material inside the body, it must demonstrate biocompatibility through testing and analysis. Biocompatibility is the extent to which a material is compatible or friendly with the body. Titanium alloy, cobalt chromium, and stainless steel are considered biocompatible by the FDA. However, they all corrode and can cause complications inside the body.

A concern has recently been raised in the biomedical field about the possible propensity for cobalt-chromium to cause cancer. Cobalt-chromium consists of the elements cobalt, chromium, nickel and molybdenum. There is a concern that the corrosion of cobalt-chrome in the wet, salty surroundings of the human body may be creating toxins streaming into the body, possibly causing cancerous tumors. Even though only about 15 tumors have ever been reported at the site of an implant, many more can exist and go unreported (partially due to the age of most patients). Although these concerns have met some strong opposition in the industry, many companies are pushing towards safer materials: Titanium, inert fiber-reinforced composites, and ceramics. Studies involving titanium have demonstrated that this material is generally well tolerated in the body.

Skin condition such as dermatitis has been reported from exposure to nickel. Cobalt shows signs of causing anemia by inhibiting iron from being absorbed into the blood stream. Ulcers and central nervous system disturbances have been detected as a result of chromium. The presence of aluminum in some implant materials may cause epileptic effects and Alzheimer's disease. Most of these side effects are result of testing done outside the body in a different state from the implant. However, they do indicate the possible hazards associated with the corrosion of implant materials inside the body.

Because all metals corrode, 100% prevention of corrosion is impossible. The only apparent solution to reduce the corrosion is to select better quality materials. Efforts

should also be made to use materials whose corrosion does not create adverse effects inside the body. The common denominator of these types of complications is that all these increase pain and reduce the functional capacity of the implant. This leads to a subsequent loss in quality of life of the patient. Thus, the complications prevent THR from achieving its goal.

10.4.2.3 PROPERTIES OF COBALT CHROME ALLOYS

For nickel-chrome alloys, it is known that a chromium content of at least 20% is required for these alloys to be corrosion-resistant and biocompatible. Chromium protects the metal underneath through the formation of mechanically and chemically stable oxide layers. This is comparable to painting a garden fence. The paint prevents the penetration of air, water and acids to the metal in the fence. However, one needs a certain amount of paint to ensure a complete coat. In the case of nonprecious alloys, chromium corresponds to the paint and the chromium concentration corresponds to the quantity of paint. In DIN-13–912, a minimum chromium concentration of 20% is required in the composition. Furthermore, it is assumed that a value greater than 30 (Wirobond®C: 54.05) should be attained through the formula "Cr content + 3.3 * (Mo content + 0.5 * W content)."

A carbon content of <0.02% ensures that no carbide precipitation occurs during laser welding. This would then result in an increased risk of fracture.

Highly pure base metals are used to make alloys. However, there are no 100% pure metals. For example, platinum ores contain palladium and sometimes also nickel impurities, cobalt is accompanied by nickel (and conversely), etc. Complete separation of the elements is never possible. The relevant standards (3, 4) stipulate a maximum nickel content of 0.1%. Alloys with less than 0.1% of nickel can be designated as nickel-free. In the case of Wirobond®C, the CE mark guarantees that the nickel concentration is less than 0.1%.

If a restoration made of a cobalt-chrome alloy weighed 10 g (extremely large bridge, partial denture), the entire restoration would contain a maximum of 0.07 g (= 70 mg) of nickel. The latter, however, is not only found on the alloy surface, but is spread homogeneously throughout the restoration. If one assumes that nickel is detached from the alloy to the same extent as cobalt, the release of nickel will amount to about 0.03 µg/cm² in the first week and will constantly decline thereafter. If one compares this to the daily uptake 190–900 µg in the food, toxicological or allergic stress appears very improbable. In the case of alloys with veneering capacity, the available area is additionally reduced considerably due to the veneered ceramics. Mechanical properties of cobalt-chrome alloy are shown in Table 3.

With a coefficient of thermal expansion of 14.2 (10^{-6} * K^{-1}), Wirobond®C is optimally suited for conventional ceramics, such as Omega-900. This veneering ceramic is well suited for palladium-free gold alloys because of the reduced firing temperatures. Experimental studies have shown that sufficiently high bond strength can be achieved. Shear bond strength >25 Mpa, determined by means of the so-called Schwickerath Test (10), is regarded as clinically adequate. These values are surpassed by Wirobond®C with various ceramics and even after repeated casting.

The somewhat higher values for Bio PontoStar®, an alloy with a high gold content that can be veneered, can be generally viewed as positive, but presumably no longer have any clinical relevance.

As far as acrylic veneering is concerned, nonprecious alloys generally display higher values than precious-metal alloys. Wirobond®C can be used for veneering crowns and bridges with ceramics. The dental processing of cobalt-chrome alloys is assessed as more unfavorable in comparison to gold alloys. This is also reflected in the slightly higher costs for the required instruments.

This partially offsets the price advantage of the alloy. In the veneering of frames, the difference in the required processing between gold and cobalt-chrome alloys with veneering capacity is not very great. In the case of fully cast crowns, the more difficult processing of the cobalt-chrome alloys is a significant negative factor. It is recommended, therefore, that the processing instructions must be followed. Each alloy has its specific features that must be taken into account. This applies to nonprecious alloys as well as to precious-metal alloys.

10.4.3 ZIRCONIA

Zirconia as a pure oxide does not occur in nature but it is found as baddeleyite and zircon ($ZrSiO_4$) that form the main source for the material. Of these two, zircon is most widespread but it is less pure and requires a significant amount of processing to yield zirconia. Mechanical properties of Zirconia are shown in Tables 4 and 5.

10.4.3.1 APPLICATION OF ZIRCONIA IN ORTHOPEDIC IMPLANTS

Zirconia is used for femoral head component in hip implants. High strength and high toughness allow the hip joint to be made smaller that allows a greater degree of articulation. The ability to have a high surface finish allows a low friction of the joint and manufacturing for articulating joints such as hip.

The chemical inertness of the material to the physiological environment reduces the risk of infection. Alumina and Zirconia are known for their general chemical inertness and hardness. Figure 1 shows effects of fracture toughness on flexural strength for ceramics.

These properties are exploited for implant purposes, so that it can be used for an articulating surface in hip and knee joints. It is an ideal candidate for the wear application, where it operates against materials such as ultra high molecular weight polyethylene (UHMWPE).

Alpha-Alumina and partially stabilized Zirconia (**YPSZ**) are accepted and standardized ceramic materials in clinical use today, and have a long clinical history in hip joint replacement in articulation with Polyethylene or themselves (Alumina). Although effective, both materials have specific potential disadvantages. Alumina exhibits excellent hardness and wear properties, however, it is a brittle material with a risk of fracture. Therefore, there are certain design restrictions. Zirconia has only 50% hardness compared to Alumina, but transformation toughening improves fracture resistance. Therefore, its overall toughness and bending strength are substantially higher than Alumina. However, because Zirconia is in a met stable form, phase transition can occur and affect its overall stability. The poor thermal conductivity of Zirconia

is a concern. Therefore the ideal ceramic would be a material that combines the best properties of Zirconia and Alumina.

TABLE 3 Mechanical properties of Cobalt chrome (8).

Property	Units	Value
Ultimate strength	MPa	931
Modulus of elasticity	GPa	232.8
0.2% ductile yield	MPa	414
Elongation limit	%	70
Shear modulus	GPa	83.36
Melting point	˚C	1315–1440
Thermal conductivity at 316˚C	W/m-k	17.0
Poisson ratio	—	0.29

TABLE 4 Mechanical properties of zirconia ceramics (28).

Zirconia Ceramics (*at 20˚C)				
Property	**Units**	**PSZMg**	**PSZYt**	**FSZYt**
Stabilization	—	MgO	Y_2O_3	Y_2O_3
Stabilization percent (mole)	%	5.0	3.0	8.0
Bulk density*	g/cm^3	5.70	6.00	5.70
Flexural (Bending) strength*	MPa	620	850	140
Elastic modulus *	GPa	200	200	—
Hardness*	kg/mm^2	11.5	12	—
Fracture toughness*	$Mpa_*m^{1/2}$	11	8	—
Porosity*	%	0	0	0

TABLE 5 Mechanical properties of zirconia.

Property	Units	TZP f	PSZ f	Y-CSZ f	Mg-ZrO_2 g
Matrix density	g/cm^3	6.0	5.7	5.9	5.5
Porosity	%	< 1	ca. 15	< 1	ca. 30
Mechanical properties					
Crushing strength 20°C	MPa	2100	ca. 2000	ca. 1800	ca. 1600

TABLE 5 *(Continued)*

Property	Units	TZP f	PSZ f	Y-CSZ f	Mg-ZrO_2 g
Flex-cracking 20°C	MPa	1200	ca. 600	300	ca. 200
Resistance at 800°C	MPa	350	—	—	–
Modulus of elasticity	GPa	200	190	170	—
Fracture toughness, K1C	MPa Ö m	10	6	3	—
Vickers hardness	GPa	13	——	——	——
Thermal shock resistance	——	low	medium	low	good

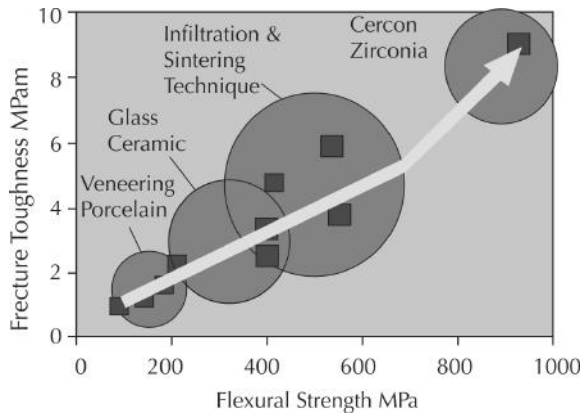

FIGURE 1 Fracture toughness versus flexural strength for ceramics (28).

10.4.3.2 ZIRCONIA STRENGTH AND RELIABILITY

High strength is important in a framework material, but strength alone is not sufficient to create a viable restoration. The resistance of a ceramic to failure through the growth of small cracks (toughness) is a best predictor of clinical success in a dental material. Zirconia is unique among dental ceramics in that it exhibits a physical property called transformation toughening (strengthening). In high stress zone of a crack tip, Cercon zirconia goes through a phase transformation to a different, larger volume structure of zirconia. This process acts to effectively resist crack growth, and toughen the material locally. This transformation toughening process is an important property of the Cercon zirconia. No other dental ceramic exhibits this phenomenon. In practical terms, zirconia is a viable choice for a reliable bridge restoration in the molar region. Zirconia (Table 4) based materials are characterized by:

1. High strength.
2. High fracture toughness.
3. High hardness.
4. Wear resistance.

5. Good frictional behavior.
6. Non-magnetic.
7. Electrical insulation.
8. Low thermal conductivity.
9. Corrosion resistance in acids and alkalis.
10. Modulus of elasticity similar to steel.
11. Coefficient of thermal expansion similar to iron.

10.4.3.3 ESTHETICS AND BIOCOMPATIBILITY OF ZIRCONIA

Only a high-strength ceramic, such as Cercon Zirconia, can provide a reliable, biocompatible and esthetic solution for all crown and bridge restorations. Cercon Zirconia is a highly stable oxide ceramic. It has a history as a biomaterial dating back to the 1970s, and is currently the material of choice for use in total hip replacements. Cercon Zirconia has a unique combination of excellent physical, mechanical and chemical properties. The zirconia framework material Cercon base and the veneering porcelain Cercon ceramic combine to form a restoration that mimics the natural vital tooth in appearance, behavior and longevity. Cercon ceramic porcelain features engineered compatibility to Cercon base, as well as high translucency, vitality and light dynamics.

10.4.4 STAINLESS STEEL

Stainless steel (SS) is essentially low carbon steel that contains chromium. The corrosion resistance and other useful properties of the SS are enhanced by increased chromium content and the addition of other elements such as molybdenum, nickel and nitrogen. The alloys used in orthopedic surgery need to have certain specific properties. Since the alloy will be bathed in body fluid, it is imperative that a low rate of corrosion and relative inertness be specific to the material. For orthopedics, SS-316L is used. The stainless steel type 316L was accredited to Sherman Surgical stainless steel alloys; they discovered this specific material that is made with varying amounts of iron, chromium, and nickel. The "L" grades are used to provide extra corrosion resistance after welding. The letter "L" after a stainless steel type indicates low carbon (as in 316L). The carbon is kept to 0.03% or less to avoid carbide precipitation. Carbon in steel when heated to crtical temperature range (800 to 1600° F), it precipitates out and combines with the chromium causing collection on the grain boundaries. This deprives the steel of the chromium in solution and promotes corrosion adjacent to the grain boundaries. By controlling the amount of carbon, this is minimized. For welding ability, the "L" grades are used. "L" grades are more expensive.

The low carbon (L) in surgical stainless steel improves corrosion and decreases adverse tissue response and metal allergy. These allergies can produce some reaction in the body. The steel can form a battery effect when it is mixed with the body fluid. Those solutions can react against the implant so that the scientist will make some arrangements to the materials properties.

The only difference in composition between SS-316L and SS-316 is the content of carbon. A wide range of properties exists depending on the heat treatment (annealing to obtain softer materials) or cold working (for greater strength and hardness). Even the SS-316L may corrode inside the body under certain circumstances in a highly

stressed and oxygen depleted region, such as contact under screws or fracture plates. Thus, stainless steels are suitable to use only in temporary implant devices, such as fractures plates, screws and hip nails.

10.4.4.1 TYPES OF STAINLESS STEEL

TYPE 304: It is a most commonly specified austenitic (chromium-nickel stainless class) stainless steel. This grade withstands ordinary corrosion in architecture, is durable in typical food processing environments, and resists most chemicals. Type 304 is available in virtually all product forms and finishes.

TYPE 316: Austenitic (chromium-nickel stainless class) stainless steel contains 2%-3% molybdenum (whereas 304 has none). The inclusion of molybdenum gives 316 greater resistance to various forms of deterioration.

TYPE 409: Ferrite (plain chromium stainless category) stainless steel is suitable for high temperature applications. This grade has the lowest chromium content of all stainless steels and thus is the least expensive.

TYPE 410: Most widely used is martens tic (plain chromium stainless class with exceptional strength) stainless steel: featuring high level of strength conferred by the martens tics. It is a low-cost, heat-treatable grade suitable for nonsevere corrosion applications.

TYPE 430: The most widely used is ferrite (plain chromium stainless category) stainless steel, for general-purpose corrosion resistance, often in decorative applications

The purity of the refined implant alloy may influence greatly the corrosion resistance and mechanical properties. All steels contain impurities or nonmetallic inclusions, which are minimized to obtain the desired combination of properties for implantation purposes. It is estimated that stainless steel alloys constitute approximately 60% of the implants used in the United States. A wide range of properties exists depending on the heat treatment (annealing to obtain softer materials) or cold working (for greater strength and hardness).

10.5 ORTHOPAEDIC HARDWARE

The surgeons must exercise caution when adjusting patients with orthopedic hardware in the region intended for adjustment. The first consideration should be to assess the stability of the region. Orthopaedic hardware can loosen – even fracture – due to biomechanical stresses and infection. Scientists are able to assess biomechanical changes as they appear on plain films. However, we are not so familiar with the radiographic changes associated with orthopedic hardware; we should be aware of the problems associated with it, especially if we are going to treat patients with orthopedic fixation devices.

The radiograph is a most effective way of assessing the stability of a fixation device. Following considerations should be taken into account while performing radiographs of orthopedic fixation hardware:

A. Technical considerations for X-rays of orthopedic hardware are:

- Expose a *minimum* of two orthogonal views of the body part.
- Include the entire body part on the film, including the joints above and below.
- Include the entire orthopedic device, preferably with several centimeters of normal bone on either end.
- Include a slight overexposure, which may be helpful for looking at metal fixation devices.
- Compare with old films, which is mandatory if there is a healing fracture.

Though the patients may already be under the care of orthopedic surgeons, yet the chiropractor should carefully look for problems of fixation for general safety. Specifically, look at the alignment, apposition and rotation of the region under assessment. Always look for problems with the fixation device: Incorrect application of the device, device failure, or infection of the device.

Be familiar with the general names and function of the various orthopedic devices that are used by the patients. If one is generally aware of the particular function of the device, evaluating the stability of the region is much easier. Avoid counterrotation and the use of the area with the device as a fulcrum. This is just a general rule of thumb, but it makes sense not to stress an area that might be weak anatomically. One might need to modify or completely avoid some adjustment techniques.

B. Classification of orthopedic fixation devices:

INTERNAL FIXATION DEVICES:

- Screws
- Plates
- Wires and pins
- Intramedullary rods and nails
- Spinal fixation devices

EXTERNAL FIXATION DEVICES

- Fracture fixation
- Radius
- Tibia
- Pelvis
- Bone lengthening
- Ilizarov device

The chiropractors do not worry about the external fixation devices, because a chiropractor would not adjust a patient with these types of contraptions in place.

10.5.1 SCREWS

The mainstay of orthopedic fixation is the screw. An "Atlas of Rush Pin Techniques by Berivon" is available free of charge by calling 1–800–251–7874 and is recommended. The screw can be used alone or along with other devices. The main function of the screw is to compress the fragments together. This can be static or dynamic (where the body's weight or muscle forces produce added compression). **The Rule of Thumb**: patient will heal better if the fracture fragments are aligned and pressed closely

together. The idea is to stabilize the fracture and keep the bone in anatomic alignment. Screws do not protect fractures from bending, rotation or axial loading forces. Alternate devices are used to provide these functions.

One of the current tenets of orthopedic fixation is that bone heals better if the fracture fragments are pressed firmly together. Many orthopedic devices are designed to do just that, as well as their primary function of stabilizing the fracture in anatomic alignment. Fracture compression increases the contact area across the fracture and increases stability of the fracture. It also decreases the fracture gap and decreases stress on the orthopedic implant. This compression can be static, where the compression is produced by the fixation device alone, or dynamic, where body weight or muscle forces are used to produce additional compression.

In order to use a screw, one has to make a screw hole in the bone or in the hardware. One screw hole passing through both cortices of a femoral shaft may weaken the femur by 90% due to some type of stress. Figures 2 to 11 indicate different types of screws. Washers (Fig. 6) are used in two situations: To distribute stresses under a screw; and use of serrated washers to affix avulsed ligaments, small avulsion fractures or comminuted fractures to the main bone. Common types of screws are shown in Fig. 7a. An example of an invisible screw to X-ray is shown in Fig. 7b.

Lag screw is used to achieve interfragmental compression. These screws do not protect fractures from bending, rotation or axial loading forces, and other devices should be used to provide these functions.

The dynamic hip screw (DHS) resists angular deformation. However, it permits an early fracture impaction. This device is specifically designed to treat intertrochanteric fractures, but is occasionally used to treat subtrochanteric fractures as well. Like the blade plate, it has a side plate that is attached to the distal femur with several cortical screws. Cortical screws tend to have fine threads all along the shaft, and are designed to anchor in cortical bone. Rather than a blade, this plate has a hollow metal barrel through which a large lag screw is placed. This large lag screw is placed so that it bridges the femoral fracture. Ideally, this lag screw should go right down the center of the femoral neck, and its tip should be in the subchondral bone of the femoral head. The hollow barrel of the side plate holds the lag screw, and hence the femoral neck and head at an anatomic angle for healing. It also allows the lag screw to slide distally as the ends of the fracture impact and the fracture fragments move closer together. When followed over time, is quite common to see evidence of this impaction as the lag screw telescopes down into the barrel of the side plate. The average amount of impaction seen with these devices is about 7 mm. These devices can fail just like any other device. The cortical screws holding the sideplate to the bone may come loose. The sideplate may fracture at a screw hole. The lag screw may perforate the articular surface of the femur. These complications and many more await the eagle-eyed radiologist.

The DHS can be used to bridge fractures of the well-vascularized intertrochanteric area. However, when the fracture occurs a bit more proximally in the femoral neck, parallel screw fixation is often used instead. The parallel screws will cause minimum trauma to the tenuously supplied proximal head and neck fragment than a larger screw such as the DHS. If the screws are placed parallel to each other, they can allow the fragments of bone to impact together, much as a DHS will. Another type of pin used

currently at Harborview is the percutaneous pin. They are commonly used there to treat humeral neck fractures. These pins have a self-threading screw tip and are placed under C-arm fluoroscopy.

Cancellous screws tend to have coarser threads, and usually have a smooth, unthreaded portion that allows it to act as a lag screw. These coarser threads are designed to anchor in the softer medullary bone.

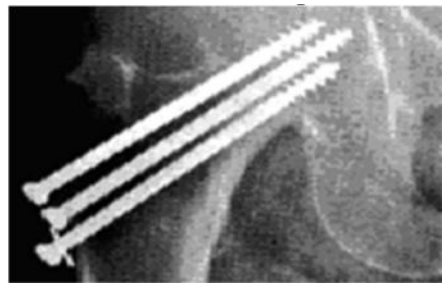

FIGURE 5 Cancellous screws to provide compression at the subcapital fracture sit (Note: The washer in the head of the inferior most screw).

FIGURE 6 A washer from 7 to 13 mm.

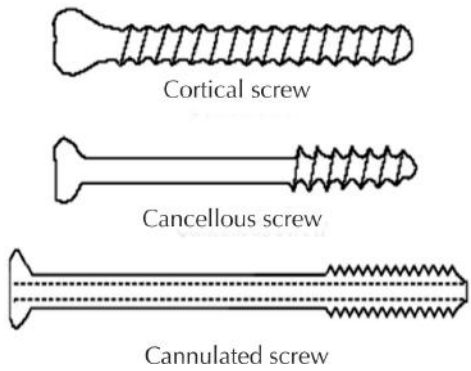

FIGURE 7A Coomon types of screws (Top).

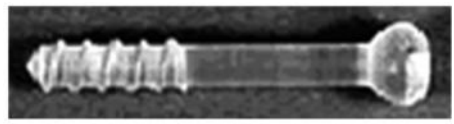

FIGURE 7B Stealth screw (Made of radiolucent polycarbonate material, eventually absorbed by the body) to reattach simple fracture fragments to the parent bone (4).

The cannulated screw with a hollow shaft can be placed very precisely. First, a wire is placed in the area of interest; then the cannulated screw is driven into the bone along the shaft of the wire; then the wire is withdrawn. With this technique, it is possible to perforate the articular surface. The cannulated screw with a hollow shaft have somewhat diminished pullout strength compared to conventional screws. Cannulated screws have many advantages over other screws, especially the precision with which they can be placed. To place these screws, the orthopaedist first drills a small Kirschner wire across the area of interest under C-arm fluoroscopic control. These "K" wires can be placed and replaced with minimal trauma to the bone until they are in optimal position. The cannulated screw is then placed over the wire and slid down to the bone surface. A special driving tool then allows the screw to be driven into the bone along the shaft of the K-wire, in a manner very similar to the way radiologists pass angiographic catheters over guide wires using the Seldinger technique. The K-wire is then withdrawn. One major complication of these screws is perforation of the articular surface when these screws are placed into a bone with their tips close to the subchondral bone. If an orthopaedist is concerned about this possibility during surgery, contrast material may be injected through the hollow center of the screw in question: Spillage into the joint cavity under fluoroscopy will be unequivocal evidence of perforation.

Specialty Screws*:* The Herbert screw is designed for use in fractures of small articular bones (Fig. 10), such as the carpals. It is cannulated and threaded at both ends. These threads run in the same direction, but the proximal portion has a wider pitch to its thread. Thus, when the proximal threads engage in the bone, they tend to move through the bone faster than the threads at the distal end, causing the two ends of the bone to compress together. This screw is used where a standard screw would impinge on adjacent tissues, such as in the treatment of scaphoid or osteoarticular fractures. The interference screw (Fig. 11) is sometimes used in the repair of the anterior cruciate ligament (ACL). In this type of repair, the surgeon employs a cadaveric allograft ligament, which has a block of bone still attached at both ends. A tunnel is drilled through the distal femur and the proximal tibia, and these bony blocks are placed within the tunnels. The interference screws are placed alongside the bone blocks so that they tightly wedge them into the side of the tunnel and prevent them from moving.

In order to use the screws, one must make a screw hole in the bone or in the hardware. The screw holes generally weaken the material they pass through. The bones and metal will tend to fracture at these sites. There are several ramifications to this for the orthopaedist and radiologist. First, since these holes weaken bones and orthopedic hardware, we should look closely at these areas on the films. Second, orthopedic hard-

ware is generally removed as soon as possible so that these holes can fill in with new bone formation and bring the bone strength back up to normal.

10.5.2 WIRES

Generally referred to as the Kirschner or "K" wires, these are very handy devices. Besides their usage with cannulated screws, they are used in many other ways to help reduce and stabilize fractures. A K-wire is essentially an unthreaded segment that is drilled into bone like a drill bit.

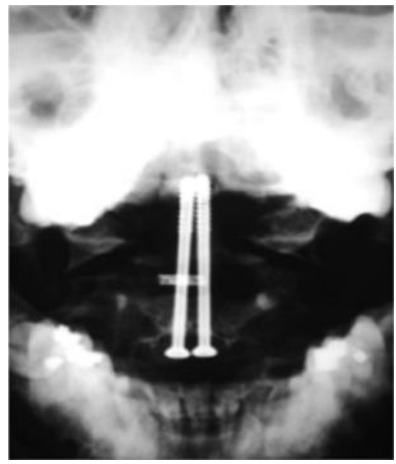

FIGURE 8 AP view: The craniocervical area, showing cannulated screws bridging a type II dens fracture (4).

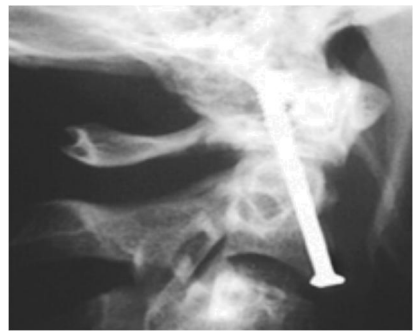

FIGURE 9 Lateral view: The craniocervical area, showing cannulated screws bridging a type II dens fracture (4).

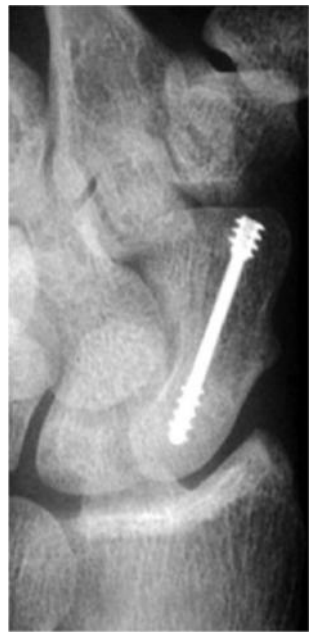

FIGURE 10 Herbert screw bridging a navicular fracture (4).

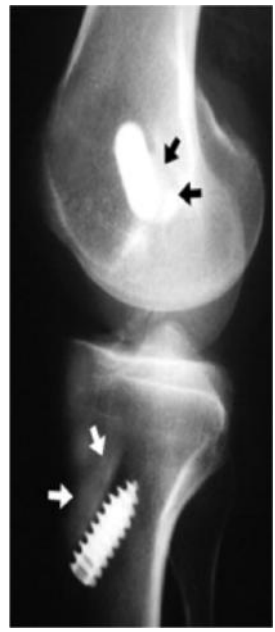

FIGURE 11 Interference screws affixing a cadaveric ACL graft. The arrows point out the pieces of cadaveric bone at both ends of the graft (4).

The major advantage of a K-wire is that it is very small and relatively noninvasive. It can be placed through an articular surface, or even across an open epiphyzeal plate without injury. K-wires can be used for either temporary or final stabilization. They can be placed between bones (Fig. 8), or they can be used as an intramedullary device to bridge a fracture of a small tubular bone. They are commonly used to help piece together all of the fragments of a comminuted fracture prior to placement of the final fixation device, especially with an intraarticular fracture.

The cerclage wire (Figs. 12a and 12b) is placed around the circumference of the bone to pull various fracture fragments together. In Fig. 12, two cerclage wires are used in conjunction with an intramedullary nail to provide support for the comminuted fragments above the transverse fracture.

A tension band wiring (Fig. 13) may be placed either by itself or in conjunction with a screw or Kirschner-wire. These tension band wires perform a sort of "biomechanical judo," because they take the normal muscular pull-to-pull the fracture fragments apart, and it is used to force the bony fragments together in compression. This same sort of biomechanical judo is employed when the tension band wire is used with a wire or screw. In Fig. 13, the reader can see that the actual location of the tension band wire is important. If the wire is placed too far posteriorly (left, Fig. 13), the muscular pull on the wire will cause the fracture to gape open anteriorly (distraction). When the wires are placed far enough anteriorly (right, Fig. 13), the muscular pull causes the patellar fragments to be pushed firmly together in compression. A fracture is possible through the olecranon process. In a situation like this, the triceps muscle group will exert a large force tending to pull the proximal fragment far away from the rest of the ulna. Even when the fracture has been bridged by one or more screws, there is a tendency for these screws to be pulled out by the triceps. The addition of a tension band wire (Fig. 14) will convert some of the triceps traction into compression at the ends of the bone and prevent the screw from pulling out.

The Kirschner or "K" wires are a handy device in the hands of the (Fig. 15) orthopaedist. Besides their usage with cannulated screws, they are used in many other applications to help reduce and stabilize fractures. A K-wire is essentially an unthreaded segment of extruded wire which is drilled into bone like a drill bit. The major advantage of a K-wire is that it is very small and relatively noninvasive as hardware goes. It can be placed through an articular surface or even across an open phyzeal plate without injury. K-wires can be used for either temporary or final stabilization. They can be placed between bones or they can be used as an intramedullary device to bridge a fracture of a small tubular bone. They are commonly used to put togather all the fragments of a comminuted fracture prior to placement of the final fixation device, especially with an intraarticular fracture.

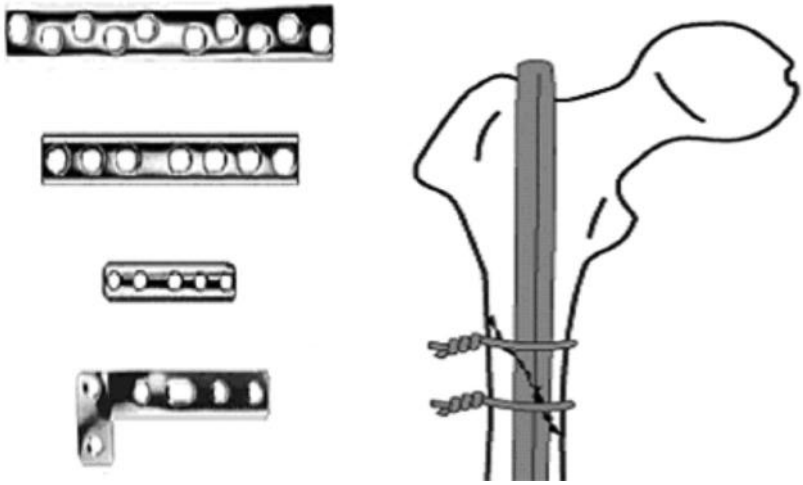

FIGURE 12 Left, Fig. 12a: Plates (19). Right, Fig. 12b: Femoral fracture bridged by an intramedullary nail and two cerclage wires (23).

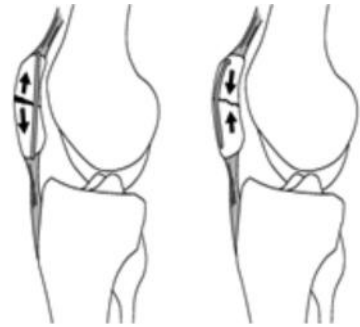

FIGURE 13 Patellar fracture bridged by tension band wire (19).

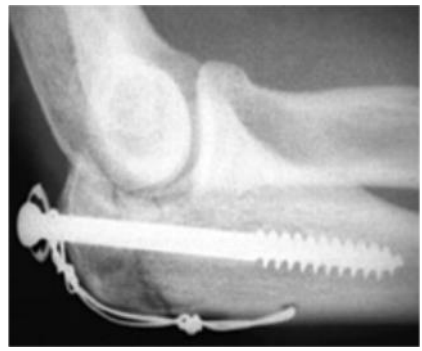

FIGURE 14 Olecranon fracture bridged by cancellous screw and tension band wire.

10.5.3 PLATES

Plates come in several types (Figs. 16 to 23): Compression, neutralization and buttress plates. For more details, the reader can refer to online source at: <http://www.rad.washington.edu/academics/academic-sections/msk/teaching-materials/online-musculoskeletal-radiology-book/orthopedic-hardware>. Compression plates are used for fractures that are stable in compression. They may be used in combination with lag screws, and they may provide dynamic compression when used on the tension side of bone. The dynamic compression plate (DCP) is one of the most common types of plates, and can be recognized by special oval screw holes. These holes have a special beveled floor with an inclined surface. If desired, this inclined surface can be used to pull the ends of the bone together as the screws are tightened. Table 6 shows the guidelines when the plates can be removed.

TABLE 6 Guidelines to remove the metal plates.

Metal plate	Months
Malleolar fractures	8–12
Tibial shat	10–12
Plate	12–18
Medullary nail	18–24
Patella, tension band	8–12
Femoral condyles	12–24
Shaft, single plate	24–36
Double plate: first	Ist: At 18
Double plate: second	2nd: 6 months aftet 1st
Femoral shaft and medullary nail	24–36
Hip – trochanteric and neck	12–18
Upper extremity (optional)	12–18

A low contact dynamic compression plate (LCDCP: Fig. 16) is undercut under each screw hole and between adjacent screw holes. LCDCP is distinguished from the conventional DCP. In LCDCP, whenever a plate down against the surface of a bone is clamped, the periosteal blood supply to that area is markedly diminished. Theoretically, we can expect this to slow healing of the fracture beneath that plate. The undercutting of the plate decreases the contact area that the plate makes with the bone surface. It is expected that the periosteal blood supply is increased, and the fracture is healed healing. At University of Washington (Seattle, WA 98195–7117), a new type of reconstruction plate (Fig. 18) is being evaluated to repair the pelvic and calcaneal fractures. This plate is fairly malleable, can be readily shaped and trimmed to length for support of fractures through complex bony surfaces. These are also occasionally used for posterior fusion of the cervical spine.

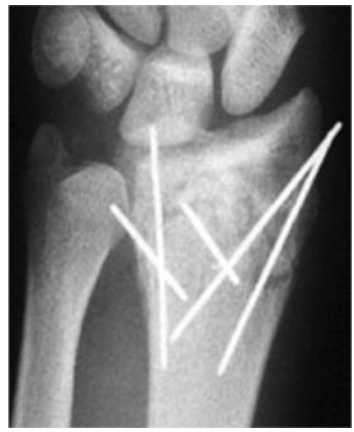

FIGURE 15 Kirschner wires ("K" wires) used to stabilize a distal radial fracture.

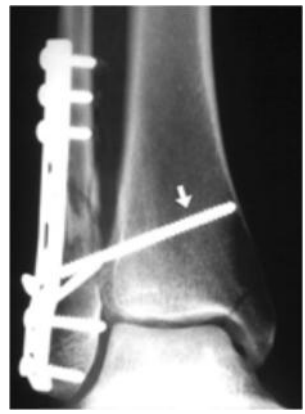

FIGURE 16 Dynamic compression plate (DCP) bridging a fibular fracture. The arrow is pointing to a syndesmosis screw, which is bridging the tibiofibular syndesmosis, whose ligaments have been torn during the injury. Also note a medial malleolar fracture bridged by a screw channel.

Neutralization plates (Fig. 29D) are designed to protect fracture surfaces from normal bending, rotation and axial loading forces. They are often used in combination with lag screws.

Buttress plates (Fig. 22) are used to support bone that is unstable in compression or axial loading. These plates are often used in the distal radius and tibial plateau to hold impacted and depressed fragments in position once they have been elevated.

The blade plate is usually shaped at an oblique or right angle and is designed to be used with subtrochanteric femoral fractures or supracondylar fractures of the femur. It is also occasionally used to bridge a femoral osteotomy. One arm of this device has a chisel-shaped end that is driven into the bone, bridging the fracture. The other arm is used as a side plate and anchored to the bone with multiple screws.

10.5.4 WASHERS

Washers are generally used in two situations. They are used to distribute the stresses under a screw head so as to prevent thin cortical bone from splitting. Serrated washers are used to affix avulsed ligaments, small avulsion fractures or comminuted fractures to the remainder of the bone.

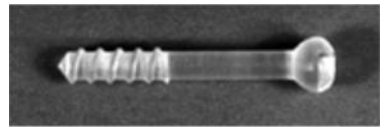

FIGURE 17 The medial malleolar fracture in Fig. 16 is held together by one of these screws, made of a radiolucent polycarbonate material, which is designed to eventually be absorbed by the body ("stealth hardware").

FIGURE 18 Low contact dynamic compression (LCDC) plate showing the typical undercutting beneath each screw hole and between each screw hole (28).

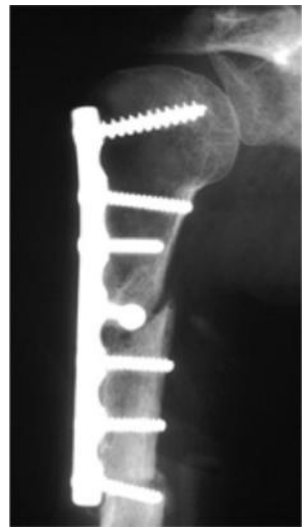

FIGURE 19 Low contact dynamic compression (LCDC) plate bridging a humeral shaft fracture – note the undercutting between each screw hole – also noted is a humeral fracture through the dist. almost screw hole (4).

FIGURE 20 Reconstruction plate (11).

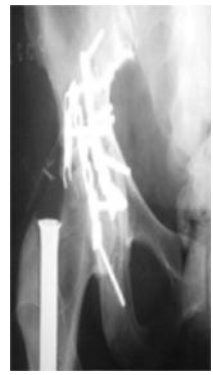

FIGURE 21 Right acetabular fracture bridged by two reconstruction plates and multiple screws. Also the proximal end of an intramedullary femoral nail can be observed (4).

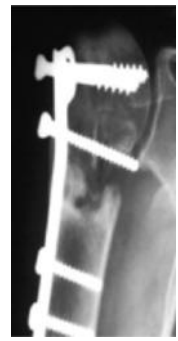

FIGURE 22 Buttress plate bridging a humeral neck fracture – note that 2 of the 3 most proximal screws have backed out (they are loose!) and that 2 of them may penetrate into the joint space (4).

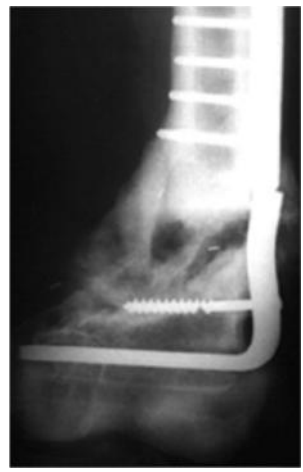

FIGURE 23 Blade plate bridging a distal femoral fracture (4).

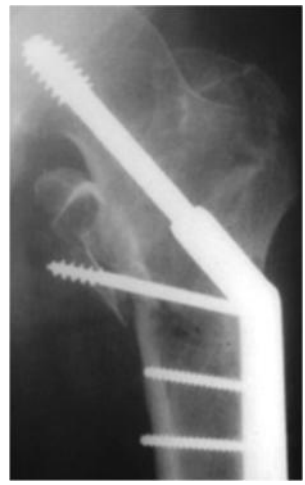

FIGURE 24 Comminuted intertrochanteric fracture of the proximal left femur bridged by a dynamic hip screw (4).

Neutralization (Fig. 29D) bridges a comminuted fracture and transmits bending or torsional forces from the proximal to the distal fragment, thus protecting the intervening fracture fragments from these forces. Applications of orthopedic hardware are shown in Figs. 28 to 42.

The sliding screw plate consists of a lag screw and a slide plate with a barrel. The threaded portion of the screw is placed in the femoral head and its shaft is inserted into the barrel of the side plate. The threads of the lag screw should be in the subchondral bone; with the screw tip optimally about one half inch from the articular surface. The side plate should lie flush with the femoral shaft and the screws attaching it to the cortex should just penetrate the far cortex. The barrel of the side plate should not be in contact with the proximal fracture fragment to ensure impaction of bone at the fracture site.

The degree of telescoping of the sliding screw is measured by noting the change in the distance from the end of the barrel to the first screw thread. Telescoping usually averages 7 mm. The leg length discrepancy of 7 mm can cause significant biomechanical changes in the pelvis and low back.

As with any device, several complications can occur: The screw can penetrate the joint; the lag screw turns out to be too short and the telescoping may be limited by contact between the threaded portion of the screw and the barrel. The telescoping mechanism may also fail due to other reasons, such as: The nail may break or bend caused by nonunion of the fracture; the screw can become disengaged from the barrel. Before manipulating any patient with the orthopedic hardware, make sure that the placement and stability of the device are adequate. Also, the technique for the orthopedic use does not affect the stability of the region.

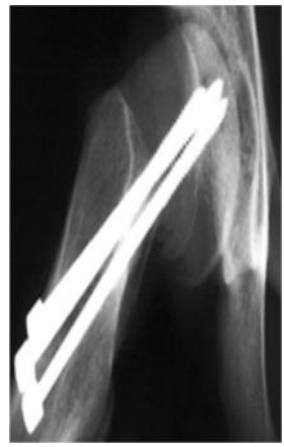

FIGURE 25 Knowles pins bridging the right phyzeal line in a patient with a slipped femoral capital epiphysis (4).

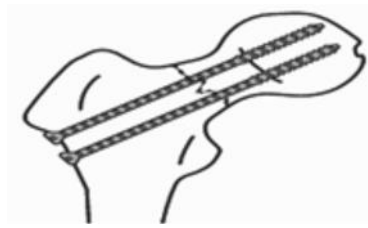

FIGURE 26 Parallel screw fixation of a femoral neck fracture with cannulated screws (28).

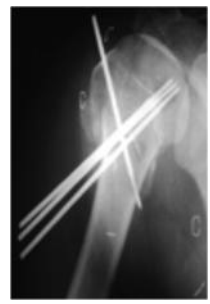

FIGURE 27 Comminuted fracture of the surgical neck of the humerus bridged by four percutaneous pins (4).

10.5.5 COMMON SPINAL FIXATION DEVICES

The venerable Harrington rod is used for spinal fixation (Figs. 37 to 42). It is used for either distraction or compression, and has hooks on either end that are designed to be placed under the lamina or traverse processes; then the device is either extended or compressed. Often they are used in conjunction with each other, and one side is

compressed while the other side is extended, as in the scoliotic spine. I'm certain you have all seen these types of devices.

Other common devices are *Weiss* springs, which are compression devices that are attached to the laminae. *Luque* rods are L-shaped, or rectangular rods that are attached to the spine by a series of wires placed around the laminae. These provide considerable stability so that the need for postoperative immobilization is reduced.

Again as with any device, it can fail, and the above are a few examples of fractured Harrington rods. If we use caution when managing patients with hardware, we will avoid causing any more injury and may even affect some relief in clinical symptoms.

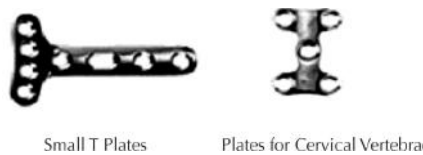

FIGURE 28 Plates: Left – Small T-plate; Right – Cervical vertebrae plate.

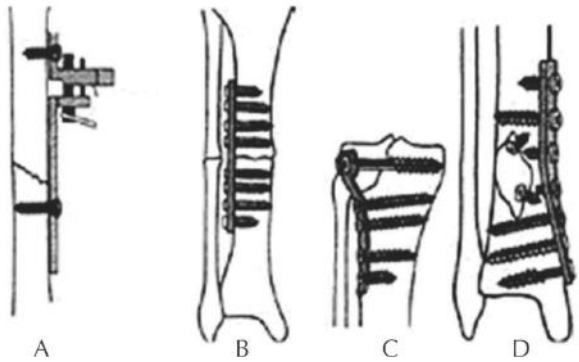

FIGURE 29 Plates: A. Static compression; B. Dynamic compression; C. Buttressing; and D. Neutralization.

10.5.6 RODS AND NAILS

There are different types of rods that can be placed into the intramedullary canal. The most common are the interamedullary rod and the interamedullary nail (Fig. 43). The nails to be placed in the medullary canal must have the canal reamed to avoid shattering of the bone as the nail is hammered down the shaft. Reaming may cause thermal osteonecrosis, compromizing the blood supply. If the medullary canal is small, a tourniquet is used during reaming, or there is marked soft tissue injury. If intraosseous pressure becomes elevated during the process, fat emboli can migrate to lungs. However, reaming is an invasive procedure. There are several devices developed for insertion without reaming the canal. The "rush" rod has a chisel-like tip, and is commonly used for fibular shaft fractures.

Another type of unreamed nail is the Ender nail (Fig. 44). These nails also have a chisel-like end. These nails are usually used three or four at a time, and pushed

through a cortical hole up or down the shaft of the bone and across the fracture under fluoroscopic control.

The odds-on favorite nowadays for fixation of fractures of the femoral or tibial shaft is a reamed or unreamed nail like the ones shown below. These nails permit early weight bearing and can be placed with closed technique, which avoids damage to soft tissue and to the periosteal and muscular blood supply. If the fracture is transverse and otherwise uncomplicated (not comminuted, rotated or too near the end of the bone), the nail may be placed by itself. However, interlocking screws are very commonly added both proximally and distally to provide stability in cases of comminution, and to prevent shortening of the bone or rotation of the fracture fragments. When these screws are used, the nail is commonly referred to as an "interlocking" nail.

FIGURE 30 The reconstruction plate to repair pelvic fractures.

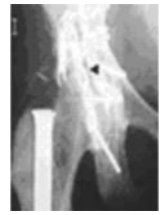

FIGURE 31 The reconstruction plate to stabilize comminuted acetabular fracture.

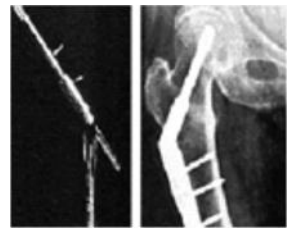

FIGURE 32 Left: Sliding screw plate with a lag screw telescoping through the barrel. **Right:** Well positioned sliding screw plate.

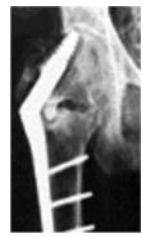

FIGURE 33 Nounion of intertrochanteric fracture with "cutting out" cpmression screw: Compression screw tip positioned in the lateral half of the femoral head

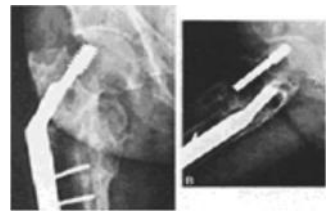

FIGURE 34 Left (A): AP view showing the screw overlying the lateral portion of the femoral head. Right (B): A frog-leg lateral view showing disengagement of the compression screw from the lateral.

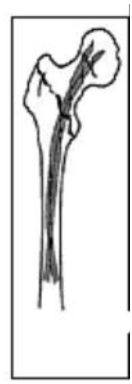

FIGURE 35 Left: Rush rods.

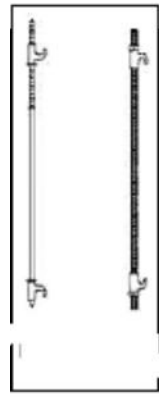

FIGURE 36 Center: Distraction and extension rods.

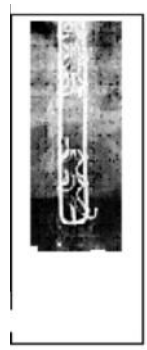

FIGURE 37 Right: Harrington rods to straighton a scoliosis.

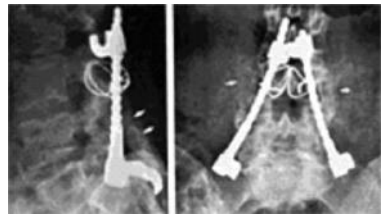

FIGURE 38 Harrington rod to stabilize a spondylolysis (left) and spondylolisthesis (right).

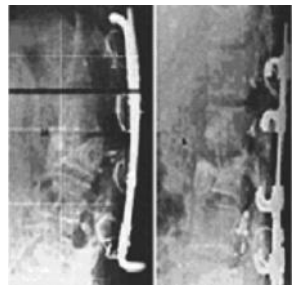

FIGURE 39 Posterior spinal fusion for an unstable vertebral body fracture. Left: A lateral view of initial postsurgical showing Lugue rods and posterior grafting. Right: Revision surgery with Harrington compression rods and posterior graft.

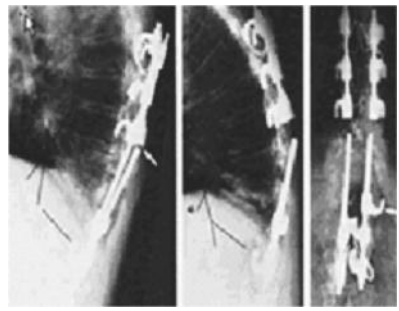

FIGURE 40 Examples. **Left:** A fractured rod. Center: Fractured rod. **Right:** Rods with a rotated hook.

Subtrochanteric fractures are difficult to treat, and they behave very differently from a variety intertrochanteric fracture. In the latter fracture type, a dynamic hip screw (DHS) can be used to provide angular support. Longitudinal support by the DHS is not as important in this type of fracture, since the ends of the bone tend to impact against each other in a stable manner. Subtrochanteric fractures exert a huge stress on a DHS, especially along the sideplate. For this reason, special nails such as the Zickel and gamma nail can be used. Both nails are more invasive. However, these nails are much stronger than the DHS, and offer a much shorter moment arm for rotational forces to act upon than the DHS.

FIGURE 41 Rush rod bridging a distal fibular fracture (14).

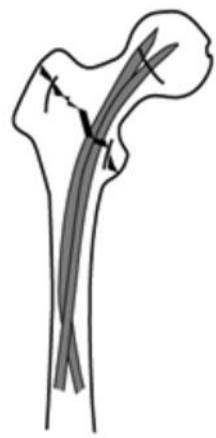

FIGURE 42 Ender nails bridging a femoral shaft fracture and an intertrochanteric fracture (14).

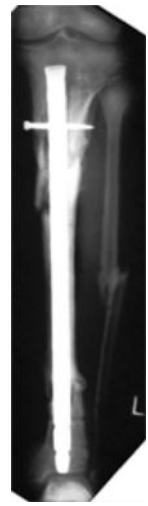

FIGURE 43 Segmental fracture of the tibia: bridged by an intramedullary nail with a proximal interlocking screw, the distal interlocking screws have been removed (4).

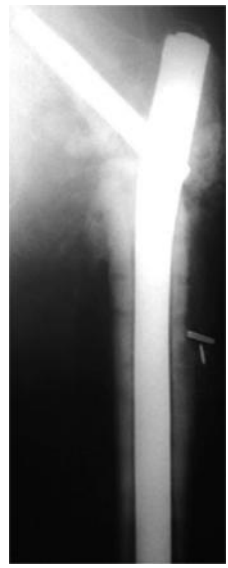

FIGURE 44 Zickel nail bridging a subtrochanteric fracture (4).

10.5.7 SPINAL FIXATION DEVICES (FIGS. 45 TO 49)

Venerable Harrington rod is a spinal fixation device (Figs. 45 and 46). These are of two types: distraction and compression. The hooks are designed to be placed under the lamina or transverse processes, and the device is either extended or compressed to the desired position. Sometimes both types of rods will be used in the same spine.

Harrington rod and Edward's rod (Fig. 47) are being superseded by other newer devices, such as: posterior spinal rod. These rods are usually used in pairs, and are attached to pedicular screws which are anchored in multiple vertebral bodies above and below the site of treatment.

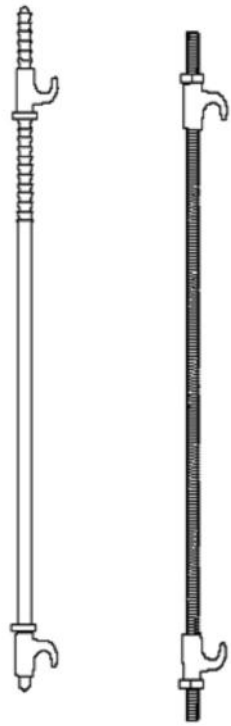

FIGURE 45 Harrington distraction rod (left) and compression rod (right).

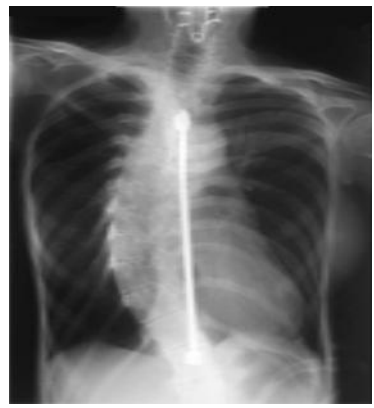

FIGURE 46 Patient with thoracic scoliosis, convex to the right, bridged by a Harrington rod and bone graft along the concave side of the spine (4).

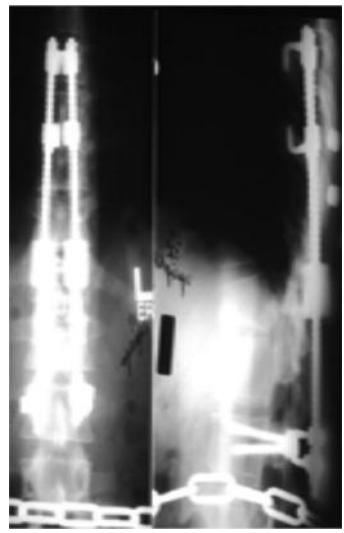

FIGURE 47 Bilateral Edwards' rods bridging a spinal fracture (4).

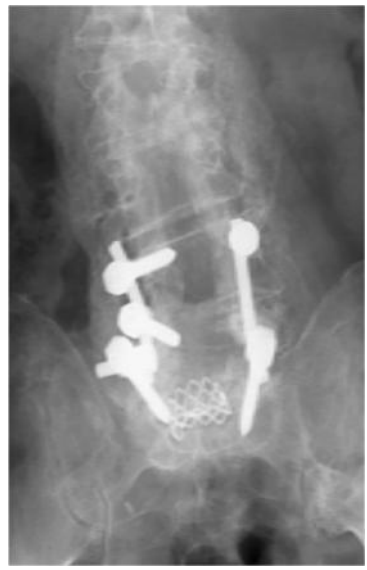

FIGURE 48 Anteroposterior (AP) of bilateral posterior spinal rods bridging L4, L5 and S1. This patient underwent spinal fusion following a laminectomy done for spinal stenosis.

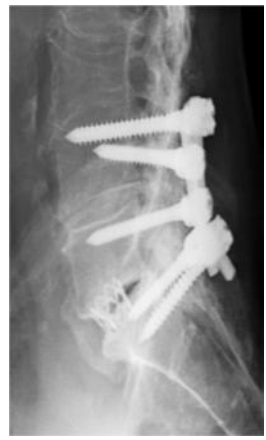

FIGURE 49 Lateral views of bilateral posterior spinal rods bridging L4, L5 and S1. This patient underwent spinal fusion following a laminectomy done for spinal stenosis. The small metal cage seen in the L5-S1 disk space contains bone graft material, which can promote osseous fusion at this site.

10.5.8 EXTERNAL FIXATION

All things being equal, orthopaedists generally prefer to treat fractures in a closed fashion. Sometimes there are extenuating circumstances that preclude the use of internal fixation. External fixation devices can be very helpful under these circumstances. Indications for external fixation are: Open fracture with massive soft tissue damage; to provide instant fixation in case of polytrauma; and may be the only way to treat fractures with deficient bone stock or infection (external fixation allows easy access to wounds).

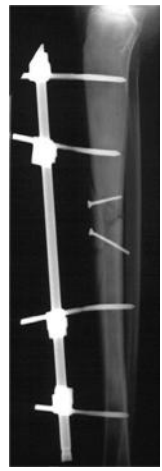

FIGURE 50 Screws are placed into the bone above and below the fracture, and a device is attached to the screw from outside the skin (28).

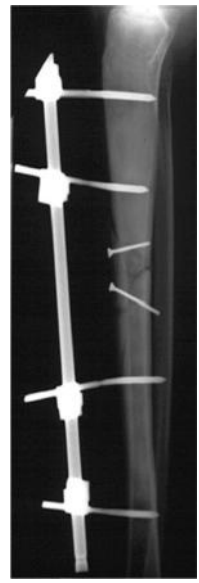

FIGURE 51 External fixator bridging a tibial fracture.

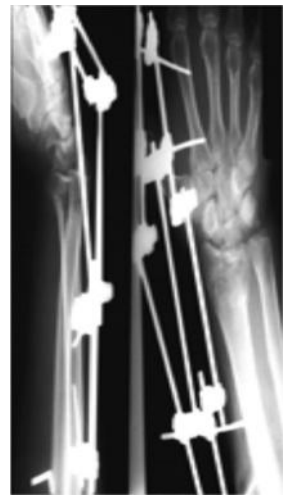

FIGURE 52 External fixator bridging an unstable distal radial fracture.

The threaded pin, anchored in the bone, is a weak link in the external fixation system. These pins should pass through the cortex on either side of the medullary space. Only a few millimeters of the pin tip should ideally protrude through the distal cortex. The usual complication of this fixation system is loosening or infection (or both) of the pins. Lucency developing in the vicinity of a pin, as it travels through the cortex, is an evidence of loosening of the pin.

Long before signs of radiographic infection develop, the orthopaedist will make the diagnosis by seeing pus oozing up along the pins as they exit the skin. Since these drilled holes are after all fractures of a sort, and fractures do produce callus even without infection. Even the presence of periosteal new bone formation about the pin tracts is unhelpful.

The pathognomonic of pin tract infection is called "ring" sequestrum sign, although the sequestrae thus formed actually are shaped like cylinders, rather than rings. As a pin tract becomes infected, the bone immediately adjacent to the pin becomes infected first, and a certain amount of it dies. The viable bone adjacent to this infected dead bone then becomes hyperemic and becomes relatively osteopenic. The infected dead bone remains at its original density. Occasionally, such a cylinder will be dense enough to also be seen when viewed at 90 degrees to the pin tract, and it presents as two parallel dense lines surrounded by lucent zones. External fixator bridging an unstable distal radial fracture is shown in Fig. 52. The typical orthopedic hardware tools are shown in Figs. 53 to 56.

10.5.8.1 POSIBLE RISKS OF EXTERNAL FIXATIONS

1. Pin tracts can be infected and must be carefully cleaned with hydrogen peroxide daily.
2. Pins inserted through muscles impale the muscle, and motion is very painful.
3. Prolonged use of the external fixator may "unload" the fracture and result in delayed or nonunion.
4. The external fixation pin inserted through a closed compartment may cause a compartment syndrome.
5. There can be a little peripheral callus formation, and the fracture site is still weak at the time of removal of external fixation. It must be protected by a cast, brace, crutches, etc. for few weeks.
6. Care must be exercised that the deep tip of the external fixation pin does not protrude very far beyond the distal cortex, or harm to important structures may result.

FIGURE 53 Assortment of implantable orthopedic surgical plates, anchors and screws.

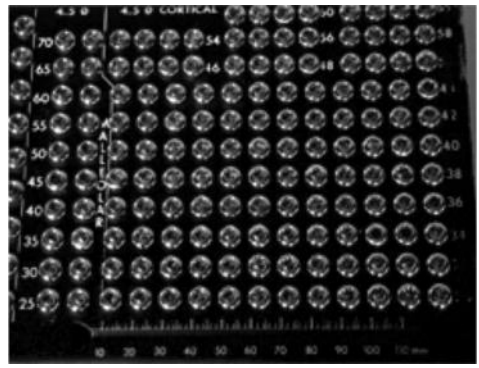

FIGURE 54 Complete set of Zimmer orthopedic and fixation screws, in sterilization case.

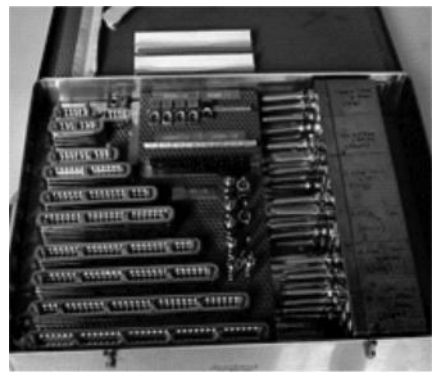

FIGURE 55 Orthopaedic Implant set.

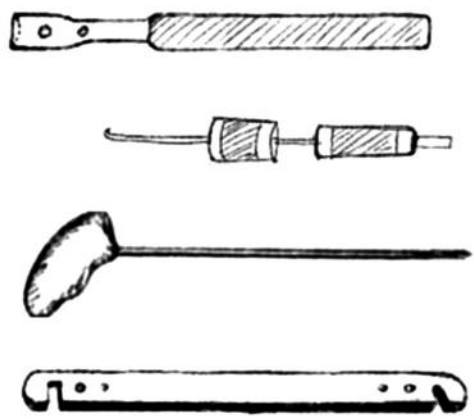

FIGURE 56 Tools for insertion. From top to bottom: rush pin driver; driver bender extractor; rush and reamer; and a bender.

10.6 ORTHOPAEDIC ALLOYS

Each manufacturer of artificial hip joints has developed one or more alloys to meet the requirement for different types of artificial joints. New metal alloys appear continually on the market and the old alloys are withdrawn. By convention the mechanical properties of a material are described in terms of the deformation or strain produced by an applied stress. Such behavior can be plotted on a stress-strain diagram. Normal stress (sigma) is defined as the applied force divided by the cross-sectional area over which it is acting. The resultant strain is the change in length per unit original length. This designation facilitates the assessment of inherent materials properties and excludes structural aspects of the test specimen. Materials are commonly evaluated in tension. However, similar although more complicated formulas exist for materials testing in compression, bending, shear, and torsion. These modes of loading represent standard methodology for materials testing and yield several parameters important to the quantitative characterization of the mechanical behavior of materials. For detailed discussion, the reader is referred to: "*Fracture Treatment and Healing* edited by B. Heppenstall. Philadelphia: WB Saunders, 1980"; and "Nag, S. and R. Banerjee, 2012. Fundamentals of medical implant materials. Pages 6–17. In: *ASM Handbbok, Volume 3: Materials for Medical Devices edited by R. Narayan*. <www.asminternational.org>." Mechanical characteristics of orthopedic alloys are shown in Table 7.

10.6.1 BIOCOMPATIBILITY

All modern alloys are well tolerated by bone tissue – in bulk form. The best tolerated is Titanium. For this extreme biocompatibility, Titanium can be used as porous coating for the surfaces of total hip prostheses. In dust form, as wear particles, all these alloys may trigger osteolysis if they land in the tissues around the total hip prosthesis. Metallic wear particles in the soft tissues paint the tissues black, and this is called metallosis.

10.6.2 METAL ALLERGY IN PATIENTS WITH TOTAL JOINTS

The metallic alloys used for fabrication of artificial joints undergo corrosion and release metallic ions into the body of a patient. Cobalt, Chromium, Nickel, but also relatively inert Titanium may evoke **allergic immune response**. The skin rash is the most often observed form of this allergy. The frequency of skin sensitivity to metals in patients with artificial joints is substantially higher than that in the general population, the percent metal sensitivity is shown below:

General population	10%
Patients with stable total joints	25%
Patients with loose total joints	60%

Some patients may have excessive skin rash reaction associated with implantation of orthopedic metal alloys. In general, such metal sensitivity probably exists in only very few susceptible patients. At this time, there is no evidence that there is an increased risk of a reaction to an implanted artificial joint in patients who have skin sensitivity. Statistical data demonstrate that many patients with a positive cutaneous (skin) test against some of the "orthopedic metals" have a well functioning total

hip prosthesis. The orthopedic surgeon, however, should be informed if the patient is allergic against any of these metals. The surgeon will also decide about the necessary postoperative tests. With the advanced technology today, the risk to patients to develop the skin rash after implantation of artificial joints may be considered minimal. The diagnosis of metal sensitivity is still difficult because of lack of reliable tests. Two questions arise:

- Is the sensitivity against metal one of the causes of failure of total hip replacement?
- Can patients with known skin hypersensitivity against any of the "orthopedic metals" (Chromium, Cobalt, and Nickel) have a successful total hip replacement operation?

TABLE 7 Comparison of mechanical properties of orthopedic alloys.

Characteristics	Units	Stainless steel	Cobalt – Chrome, Co-CR-Mo	Titanium, Ti-6Al-4 V	Titanium, pure
Stiffness	–	High	Medium	Low	–
Stength	–	Medium	Medium	High	–
Corrosion resistance	–	Low	Medium	High	–
Biocompability	–	Low	Medium	High	–
Modulus	GPa	200	200–230	110	105
	$x10^6$ psi	29	29–33	16	15
Yield strength	GPa	170–750	275–1585	850–900	692
	$x10^6$ psi	25–110	40–230	120–130	100
Ultimate tensile	GPa	465–950	600–1795	960–970	785
strength	$x10^6$ psi	65–140	90–260	140–141	115

10.6.3 FATIGUE FRACTURE OF TOTAL HIP PROSTHESIS (THP)

There is an astounding demand on biomaterials of the total hip joint. For example, a 60-year-old patient with a weight of 80 kg can live further 17 years and may expose the shaft of his total THP for 30-4 millions blows: Each blow may exert a force of 200 kg while walking, and 600 kg while running. The shaft of the modern THP can sustain such large forces. The shaft may fail even at lower cyclic loads. The metal alloy will succumb to fatigue failure and break. There is a limit on the cyclic loads that can be sustained by THP. This limit is specific for every form of THP and for the metal alloy used for the manufacturing. Above this limit, the prosthetic shaft will sustain the fatique fracture.

All modern alloys used for manufacturing of the THP are strong enough to resist failture due to fatigue fracture. Closer examination of failture cases has revealed that the fracture occurred in heavy weight patients, often after an accident. The examination of the broken shafts often revealed metallurgical defects: Scratches on the surface, defects that occured during casting, etc. Many manufactures of THP have developed

bulky models of artificial joints with larger dimensions for heavy-weight patients. Usually a patient >100 kg body weight is considered heavy-weight.

10.6.4 STRESS SHIELDING

The prosthetic shaft takes off a part of the stress that the daily activies including walking exert on the upper part of the thigh bone holding the prosthesis. A too stiff shaft of a THP may shield the upper part of the thigh bone too much. This is because the alloys used for fabrication of the shaft are much stiffer than the skeleton of the thigh bone. The shielded bone does not thrive, loses its substance, and becomes weak. The total hip joint has weak anchorage in a weak skeleton and may fail. The remedy is a prosthetic shaft manufactured from metal alloys with stiffness similar to the bone. Titanium alloy has the lowest stiffness of all orthopedic alloys and therefore shafts of cementless total hips are often made from Titanium alloys.

On the other hand, the stiffness of the prosthetic shaft depends not only on the material but also on its shape. Changing the shape of the shaft also changes its stiffness. The latest technique for less stiff THP is the "Trabecular Metal Technology" by Zimmer that designs and manufactures reconstructive, spine, sports medicine orthopedic implant devices, and THP. The company was formerly known as Implex Corporation and changed its name to Zimmer Trabecular Metal Technology, Inc. in April 2004 as the result of acquisition by Zimmer Holdings, Inc. The company was founded in 1991 and is based in Parsippany – New Jersey. As of April 23, 2004, Zimmer Trabecular Metal Technology, Inc. operates as a subsidiary of Zimmer Holdings, Inc. Trabecular Metal™ Technology (TNTZ: <http://www.zimmer.com/en-US/hcp/hip/our-science/tm-technology.jspx>) is an advanced fixation surface designed for orthopedic and dental implants. Trabecular Metal™ Material is made of elemental tantalum (atomic number 73), that is chemically stable and biologically inert, making it highly biocompatible and corrosion-resistant. Elemental tantalum can support bone integration, bone remodeling, and vascularization. Tantalum has high fatigue strength and a compressive modulus that allows it to bend before breaking. With a high coefficient of friction (0.98), it provides enhanced stability and excellent initial scratch fit: Unlike coatings and other surfaces, TMT material has up to 80% porosity, enhancing the potential for bone ingrowth and soft tissue vascularization; and with its nano-textured architecture, TMT material is similar to cancellous bone in structure, function, and physiology. TMT material has consistent pore size; 100% interconnecting pores to facilitate biologic ingrowth; low modulus of elasticity similar to cancellous bone for more normal physiological loading to reduce stress shielding. TMT material with nano-textured surface structure is in widespread use throughout Zimmer's product portfolio: Hip, knee, and shoulder implants; trauma applications; spine implants; bone void fillers and augments; AVN screws and dental implants. A metallic sponge made from Tungsten has about the same stiffness as bone. When a layer of the metallic sponge is placed on the surface of the total hip prosthesis, it will make a smooth transition from the stiff metal to the weak bone. The scientists hope that this technology will diminish the stress shielding effect of the too stiff total hip and knee prostheses.

TABLE 8 Physical and mechanical properties of Tantalum.

Property	Value	Property	Value
Density,	16.7 g.cm-^{3}	Heat of fusion,	36.6 kJ·mol^{-1}
Young's modulus	186 GPa	Bulk modulus	200 GPa
Shear modulus	69 GPa	Poison ratio	0.34
Mohs hardness	6.5	Vickers hardness	873 MPa
Brinell hardness	800 MPa	Porosity	60 to 80%
Fatigue endurance limit at 10^{8} cycles	13.2 MPa	Pore size	370 to 440 μm
Intrinsic permeability	0.21 to 0.48, nm^{2}		

10.7 RECENT ADVANCES IN ORTHOPAEDIC SURGERY

Orthopaedic Surgery has made rapid strides during the past decades. The emergence of newer subspecialities such as orthopedic oncology and pediatric orthopedics clearly reflect the diversity of clinical problems in orthopedics and traumatology. Improvements in biomaterials implant and prosthetic design, better understanding of biomechanics and improved imaging methods and surgical techniques, have contributed greatly to the progress.

10.7.1 IMPLANTS AND INTERNAL FIXATION TECHNIQUES

Interlocking intramedullary nails, which permit locking of the nail to the bone proximally and distally by screws have largely replaced conventional intramedually nailing. This permits early weight bearing in the lower limb fractures. Unlike the conventional DCPs, limited contact DCPs allow circulation under the plate and a narrow area of circumferential callous to regenerate at the fracture site. Currently most orthopedic implants are constructed of 316 L stainless steel. However, newer plates made of commercially pure Titanium or Titanium-Aluminium-Vanadium alloys are being developed to reduce the metal corrosion. Biodegradable implants made from adsorbable polyesters are currently under investigation and have been used in limited clinical applicaions.

10.7.2 JOINT REPLACEMENT SURGERY

Total joint replacement of the hip and knees are among the most successful group of surgical procedures. The Present day total hip or total knee replacements can restore near normal function in patients with severe pain or markedly limited function. Although joint replacements using bone cement have established success rate over decades, the problem of aseptic loosening remains, requiring a revision arthoplasty. Uncemented total hip replacement is today "the state of the Art" and can be done even in young patients. Total elbow and total shoulder replacements are being increasingly done and the success rates have been good.

10.7.3 CUSTOM PROSTHESIS IN BONE TUMORS

The most recent advance in the surgical approach to skeletal defects after tumor resection involves the use of custom-made prosthetic joints for the replacement of defects near the hip, knee and shoulder. An individually designed, custom made bone and joint

replacement prosthesis is the optimum method of obtaining the best possible results for the patient. These custom made prostheses are made of either titanium or stainless steel alloy.

10.7.4 ILIZAROV TECHNIQUE

The Ilizarov fixator is a circular external fixator made up of rings which are connected to the bone by K-wires or pins. The rings are connected to each other by threaded rods which permit compression or distraction of bone fragments. The technique of corticotomy involves division of the bone without disturbing the medullary blood supply. Subsequently controlled distraction of fragments can be done after a few days at the rate of 1 mm per day. This distraction induces new bone formation and this is called distraction Osteogenesis. Limb length discrepancies can be corrected successfully by this technique. The other applications of Ilizarov include the correction of complex bony deformities, arthrodesis of joints, and bone transport to bridge defects after tumor resection.

10.7.5 ARTHROSCOPY

Arthroscopy is not only diagnostic but can also have therapeutic applications. The rotator cuff injuries are treated more by arthroscopic procedures, than by open surgery.

10.7.6 SPINAL SURGERY

Inter-vertebral disc prolapsed is a common clinical problem in orthopedic practice. Open disc surgery is being gradually superseded by micro discectomym, which requires a smaller opening and an operating microscope. The other options in treatment of disc prolapsed include automated percutaneous lumbar discectomy and endoscopic disc excision. These minimally invasive techniques allow rapid rehabilitation and reduce spinal instability resulting from extensive laminectomy. Better understanding of the biomechanics of the spine has resulted in the design of newer implant system for use in spinal surgery. Use of these systems both interior and/or posterior in spinal injury along with decompression permits earlier patient mobilization. It is possible to correct fully spinal deformities such as scoliosis with the advent of modular segmental spinal instrumentation systems and intraoperative spinal cord monitoring by somatosensory evoked potentials.

10.8 CONCLUSIONS

Orthopaedic fixations include screws, pins, plates etc. In this chapter, we have discussed four biomaterials: Stainless steel, Zirconia, Cobalt-chrome, Titanium, and Tantalum.

10.9 SUMMARY

Orthopaedic is a branch of medicine that deals with the injuries, fractures, rupture and disorders of the human skeletal system. The skeletal system consists of the bones, muscles and joints of our entire system. The average human adult skeleton has 206 bones joined to ligaments and tendons to form a protective and supportive framework for the attached muscles and the soft tissues which underlie it. The skeleton has

two main parts: the axial skeleton and the appendicular skeleton. The axial skeleton consists of the skull, the spine, the ribs and the sternum (breastbone) and includes 80 bones. The appendicular skeleton includes two limb girdles (the shoulders and pelvis) and their attached limb bones. This part of the skeletal system contains 126 bones, 64 in the shoulders and upper limbs and 62 in the pelvis and lower limbs. There are only minor differences between the skeletons of the male and the female: the men's bones tend to be larger and heavier than corresponding women's bones and the women's pelvic cavity is wider to accommodate childbirth. The skeleton plays an important part in movement by providing a series of independently movable levers, which the muscles can pull to move different parts of the body. It also supports and protects the internal body organs. Orthopaedic surgery can help the patient with some fixation of broken bones, or damage joints with: Screws, pins, plates, wires, etc., depending on the area that is affected. Biomaterials like stainless steel, titanium, cobalt chrome, zirconium, and Tantalum are being used for orthopedic implants. These material needs to be strong enough to support the weight and the interacting forces that a human deals every day. Each of these materials needs to be biocompatible with the human body.

KEYWORDS

- **Amenable**
- **Appendicular skeleton**
- **Atrophy**
- **Axial compression**
- **Axial skeleton**
- **Biocompatibility**
- **Biomaterial**
- **Comminuted fracture**
- **Cortical fracture**
- **Cyclic stress**
- **Deformation**
- **Dynamic compression**
- **Fatigue Strength**
- **Fixation**
- **Framework**
- **Inertness**
- **Ligament**
- **Limb girdles**
- **Modulus of elasticity**
- **Musculoskeletal system**
- **Orthopaedic**

- **Orthopaedic fixation**
- **Peripheral nerve lesion**
- **Pharmacology**
- **Plate**
- **Polish**
- **Restoration**
- **Rigid fixation**
- **Screw**
- **Segmented fracture**
- **Skeletal system**
- **Spinal disorder**
- **Static compression**
- **Sternum**
- **Stress**
- **Surgical incision**
- **Tensile strength**
- **Tensile Stress**
- **Zirconium**

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APPENDIX I: NUMERICAL EXERCISES

1. The mass of a person is 20 kg and the diameter of the femur is 50 mm. Find the stress at the femur area for each leg.
d = 50 mm = 0.05 m; m = 20 kg; g = 9.81 m/s²
W = mg = 196.2 N
The body is symmetrical, so for each leg we have W/2 as for the action on the bone: W/2 = 98.1 N
Fa = 98.1 N and Fb = 98.1 N
For d = 0.05 m, A = π/4 d² = 0.00196 m²
σ = (Fa)/A = 98.1/0.00196 = 50051 Pa = 50 kPa

2. Find $P_{all}O_w$ that a bone can resist. The ultimate stress for the bone is 120 MPa, diameter is 40 mm, and the factor of safety is 1.

d = 0.04 m; A = Area = (π/4 d²) = 0.00126; $\sigma_{ult} = 120 \times 10^6$ Pa in tension; and

$\sigma_{ult} = 65 \times 10^6$ Pa in shear.

For brittle material: $\sigma_{allow} = \frac{\sigma_{ult}}{N} = 120 \times 10^6$ Pa and $P_{allow} = \sigma_{allow}(area) = 120 \times 10^6$ (0.00126) = 151 kPa

3. The patient with a mass of 30 kg appears in the doctor's office due to the fracture on the femur area. Determine the thickness of the plate that can sustain the load of the person without exceeding the proportional limit of the plate.

Assume: σ_{allow} for the plate is 350 N and the length of the plate is 0.25 m.

W = mg = 30 * 9.81 = 294.3 N

Each femur can carry from (w/2) to w. So for the analysis we will use the entire load.

Required area = (load transmitted)/(σ_{allow}) = 294.3/350 = 0.841 m²

A = T*(*b*) or 0.841 = T*(0.25) or T = 3.36 m

4. In exercise 2 above: Calculate the angle of twist per unit length for a bone. Assume the modulus of elasticity of 14 MPa and applied torque of 6000 N-m.

$\Theta = \{T\}/\{32*G*I_p\} = (6000 \text{ N-m})/(32(14 \text{ MPa})\{ p(40/1000)^4\}) = 50°/m$

CHAPTER 11

BIOMECHANICS OF TOTAL KNEE REPLACEMENT[1, 2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Gloria Batista, Mario Ibarra, Johanna Ortiz and Melvia Villegas) for the course on Mechanics of Matials – I, INGE4011.Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com> or visit at: http://www.ece.uprm.edu/~m_goyal/home.htm. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.

[2]The numbers in parentheses refer to cited references in the bibliography.

11.1 INTRODUCTION

The synovial joints (e.g., hip, knee or shoulder joints) are complex and delicate structures capable of functioning under adverse conditions. The performance of these joints is based on: The synovial fluid (a nutrient fluid secreted within the joint area), the optimized combination of articular cartilage, anda load-bearing connective tissue covering the bones involved in a joint. Unfortunately, human joints are degenerative due toinflammatory diseases that can cause pain and joint stiffness. Primary or secondary osteoarthritis (See Chapter 9), and to a lesser extent rheumatoid arthritis (RA, inflammation of the synovial membrane) and chondromalacia(softening of cartilage), are due tonormal aging of articular cartilage: the most common degenerative processes affecting synovial joints. In fact, 90% of the population over the age of 40 suffers from some degree of degenerative joint disease. Premature joint degeneration maybe due to: Defects in the properties of biomaterial for the joint; excessiveloadingcondition; or failure of normal repair processes.

Degeneration of weight bearing joints may requirea surgery to relieve pain and increase the mobility. Through minimum invasive technique, arthroscopic surgery (most frequently performed on knee joints) provides an efficient surgical method for diagnosis and symptomatic relief of painful joints.Using metal/plastic (polyethylene)/ or ceramic artificial materials,the replacement of diseased joint surfaces can be accomplished through arthroplastic surgery. The Arthroplasty is a surgical technique which replaces all articulating degenerated natural surfaces with artificial materials to relieve the pain and to improve joint mobility by creation of a new prosthetic joint. From early excision through interposition to replacement arthroplasty, great progress has been achieved over 170 years of orthopedic surgery.The surgery for joint prostheses is now considered as normal procedure for the diseaded joints in the human body. Total hip (THR) and total knee (TKR) joint replacements have been the principal focus of artificial joint studies.In this chapter, we will discuss biomechanics of knee joint replacements and biomaterials for knee joint prostheses.

11.2 HISTORY OF TOTAL KNEE REPLACEMENT(TKR)

The history of knee replacement is the story of continued innovation to overcome problems of wear, loosening and loss of range of motion.

1891 German surgeon Theophilus Gluck performed first knee surgery. He also experimented with a number of different materials, including harvested muscle and fat, nylon and pig bladders to cushion the knee joint and relieve pain. He is also believed to have performed the first true knee replacement surgery, using ivory to simulate the knee joint structure. The ivory joint was hinged and stabilized using plaster or metal.

1891–1950s There was little improvement in knee replacement surgery. Gluck's ivory and plaster technique was updated several times using metal and plastic components, but they were still formed into a hinge-type device that was both inflexible and prone to complication and failure.

1954 Leslie Gordon Percival Shiers, pioneer of knee replacement surgery, published the original papers in the Journal of Bone and Joint Surgery in 1954.Shiers refused to

patent the invention, anddemonstrated the procedure throughout the world, inviting other surgeons to improve upon the original idea.

1960s Following John Charnley's success with hip replacement in the 1960s,attempts were made to design knee replacements.Knee replacements with hinged implants were available.However, hinged implants did not allow bending or rotation of the knee. These would often come apart soon after surgery and had a high infection rate.Frank H. Gunston and Leonard Marmorwere pioneers in North America.Marmor's design allowed forunicompartmental operations but did not always last well.

Early 1970s In the 1970s, the "Geometric" design and Condylar Knee design by John Insall found favor.Hinged knee replacements for salvage date back to GUEPAR but did not stand up the wear. The researchers at Massachusetts General Hospital developed a rounded plastic component that closely resembled the traditional knee structure and allowed for TJR. This design is often referred to as "total condylar knee."However, only two different sizes were available.The concept of replacing the tibiofemoral condylar surfaces with cemented fixation, along with preservation of the cruciate ligaments, was developed and refined. To correct severe knee deformities, the condylar knee with posterior cruciate-sacrificing design was also introduced.By 1974, replacing the patellofemoral joint and either preserving or sacrificing the cruciate ligaments became a standard practice.

Late 1970s to early 1980s The condylar knee designs were improved to include modularity and noncemented fixation, with use of universal instrumentation.The mobile-bearing knee replacement was designed and developed by by Fred Buechel, a surgeon, and Michael Pappas, an engineer at Martland Hospital – NJ – USA. The Buechel-Pappas joint replacement system is still used today. It is still being perfected and updated.A mobile-bearing replacement allows the synthetic joint platform to rotate, as opposed to a stationary fixed-bearing joint.

Late 1990s Many surgeons began to use a minimally invasive surgery that required only a 3-to-5-inch incision. Rather than cutting down the front of the leg, damaging the slow-to-heal thigh muscle, the cuts could be made in the side of the knee, and the kneecap was pushed to the side for access. This technique allowed faster recovery and fewer complications.

2002 Dr. C S Ranawat at Lenox Hill Hospital – New York published history of total knee replacements in Journal South OrthopaedicAssoctation(11(4):218–26).He indicated that "*Today, over 19 companies in the United States distribute total knee implants of three different types: cruciate-preserving, cruciate-substituting, and TC-III. Six major companies are actively involved in designing mobile-bearing knees. Future developments, such as navigation-guided surgery, enhanced kinematics, and wear-resistant bearing surfaces with better fixation, promise a consistent evolution for the total knee replacement*."

2009 Unicondylar, or partial, knee replacements were introduced. It reduces side effects and loss of blood, because a smaller incision of up to three inches is made. According to the 2009 report by Utah Hip and Knee Center, the research is being done to

develop a knee replacement technology in which the bones actually grow into the device and are hold together.Researchers claim that this technology would create fewer complications due to knee replacement surgery.

Twenty-first century Orthopaedic surgeonsstarted to use a robotic knee replacement process using a series of CT scans to create a customized knee replacement plan based on the needs of an individual patient. It consists of a computer-assisted planning program and robotic instruments to make incisions and position implants. The robotic instruments are able to manipulate tools and implants much more accurately than the human eye. Because of the precise nature of this technology, many common knee replacement problems are avoided.

11.3 ARTHROSCOPY

An arthroscopy is a type of keyhole surgery that is used both to diagnose problems with the joints and to repair damage to the joints (For more details: <http://www.nhs.uk/Conditions/Arthroscopy/Pages/Introduction.aspx>). The procedure is mostly used on the knees, wrists, elbows, ankles and shoulders.If the patient has problems with the joints, such as swelling or stiffness, and initial imaging tests have not been able to find the root cause of the condition, an arthroscopy might be an option to look at the inside of the joint.In addition to look inside a joint, an arthroscopy can also be used to treat a range of problems and conditions. For example, an arthroscopy can be used to: Repair damaged cartilage; remove fragments of loose bone or cartilage; and treat frozen shoulder. The advantages of an arthroscopy compared with traditional open surgery include: Less postoperative pain; a faster recovery time; and a lower risk of complications.

A **joint** is the point where two or more bones meet. Joints have two main purposes: **hinge**, allowing the bones to move; and **bracke**t, holding the bones in place while also protecting and supporting them.Joints are made up of five different types of tissue: bones; tendons that are made of a tough, stringy tissue to connect muscles to bones; ligaments to connect one bone to another bone; cartilage is a tough, spongy tissue that lines the surfaces of bones and acts like a shock absorber within the joint to reduce friction and prevent damage as the bones move; and synovial fluid acts as a lubricant inside the joint.

11.3.1 AN ARTHROSCOPY PROCEDURE

During an arthroscopy, a piece of equipment called an arthroscope is used.An arthroscope is a small, flexible tube that is about the length and width of a drinking straw. Inside the arthroscope, there is a bundle of fiber optics, whichact as both a light source and a camera. Images are sent from the arthroscope to a video screen or an eyepiece so that the surgeon is able to see the joint.It is also possible for tiny surgical instruments to be passed through an arthroscope so that the surgeon can treat the condition. An arthroscopy is usually carried out under general anesthetic so that the patient does not feel any pain or discomfort.An arthroscopy is usually performed on an out-patient basis.

The surgeon makes a small incision next to the joint so that the arthroscope can be inserted. One or more small incisions are also made so that an examining probe and surgical instruments can be inserted, if necessary.

The recovery time can vary depending on the joint involved and whether it needs to be repaired.It is usually possible for a person to do light, physical activities one to three weeks after the arthroscopy. Full physical activities, such as lifting and sport, can usually be resumed after six to eight weeks.

11.3.2 KNEE ARTHROSCOPIC SURGERY

Knee arthroscopic surgery is a procedure performed through small incisions in the skin to repair injuries to tissues such as: Ligaments, cartilage, or bone within the knee joint area. The surgery is conducted with the aid of an arthroscope. Arthroscopic surgery is conducted for: Flushing or smoothing out bone surfaces or tissue fragments (lavage and debridement) associated with osteoarthritis; and for the realignment of a dislocated knee and ligament grafting surgeries. While the clear advantages of knee arthroscopic surgery lie in surgery with less anesthetic, less cutting, and less recovery time, this surgery nonetheless requires a very thorough examination of the causes of knee injury or pain prior to a decision for surgery. For detailed study, the reader may consult: 1. Canale, S. Terry, 1998. Arthroscopic surgery of meniscus. In: *Campbell's Operative Orthopaedics*. 9th ed., St. Louis, MO: Mosby, Inc.; 2.<http://www.surgery-encyclopedia.com/Fi-La/Knee-Arthroscopic-Surgery.html>.

The knee arthroscopic procedures fall into roughly two group: **Acute injuries** to destabilize the knee; and **pain management**for floating or displaced cartilage and rough bone.

11.3.2.1 ACUTE INJURIES

The acute injuries are usually the result of traumatic injury to the knee tissues such: Ligaments and cartilage through accidents, sports movements, and some overuse causes. Acute injuries involve damage to the mechanical features, including ligaments and patella of the knee. These injuries can result in knee instability, severe knee dislocations, and complete lack of knee mobility. Ligament, tendon, and patella placements are key elements of the surgery.Arthroscopic surgery for acute injuries is less controversial because clear dysfunction and/or severe instability are measurable indications for surgery and easily identifiable.

The type of treatment for acute injuries depends on a strict grading system that rates the injury: **Grades I and II** include rest, support by crutches or leg brace, pain management, and rehabilitation; **Grades III and IV** indicate the need for surgery. Acute injuries can be highly debilitating to: the four stabilizing ligaments of the knee join (the anterior cruciate ligament (ACL), the posterior cruciate ligament (PCL), the medial collateral ligament (MCL), and the lateral collateral ligament (LCL)); and to the "tracking" or seating of the patella, can be highly debilitating.The procedure includes: Repair of a torn ligament or reconstruction of the ligament; release of a misaligned kneecap; and grafts to ligaments to support smoother tracking of the knee with the femur.

More than five and a half million people visit orthopedic surgeons each year because of knee problems. Over 600,000 arthroscopic surgeries are performed annually; 85% of them are for knee surgery. One very common knee injury is a torn anterior cruciate ligament (ACL) that often occurs in athletic activity. The most common source of ACL injury is skiing. Approximately 250,000 people in the United States sustain a torn or ruptured ACL each year. Research indicates that ACL injuries are on the rise in the United States due to the increase in sport activity.

The incidence of ACL injuries in women is two to eight times greater than in men. While the exact causes are not clear, differences in anatomy, strength, or conditioning are thought to play major roles. Women also seem to be more prone to patella-femoral syndrome (PFS).The PFS is the inability of the patella to track smoothly with the femur. PFS is due primarily to development of tendons that influence the ways in which the knee tracks in movement. It can also be due to misalignments to other parts of the lower body like foot pronation. Other ligament surgeries can be caused by injury or overuse.

Knee dislocations are a focus of recent research because of the increasing frequency. Incidences range from 0.001% to 0.013% of all patients evaluated for orthopedic injuries. Many of these injuries heal without treatment and go undetected. Many people with multiple traumas in accidents have knee dislocations that go undiagnosed. Knee dislocations are of special concern, especially in traumatic injury.An early diagnosis is required for the surgery to be effective. Knee dislocations in the morbidly obese individuals often occur spontaneously and may be associated with artery injury. This surgery involves complications related to the obesity. Finally, knee dislocations have been reported to occur in up to 6% of trampoline-associated accidents.

KNEE ARTHROSCOPIC SURGERY FOR ACUTE INJURIES

The knee bone sits between the femur and the tibia, attached by four ligaments that keep the knee stable as the leg moves. These ligaments can be damaged or torn through injuries and accidents. Once damaged, they do not offer stability to the knee and can cause buckling, or allow the knee to "give way." Ligaments can also "catch" and freeze the knee or make the knee track in a different direction than its leg movement, causing the knee to dislocate. Traumatic injuries such as automobile accidents may cause more than one ligament injury, necessitating multiple repairs to ligaments.**Four knee arthroscopic procedures** relate to damage to each of the four ligaments that stabilize the knee joint movement. The four procedures are:

a. **Anterior cruciate ligament (ACL):** A front-crossing ligament attaching the femur to the tibia through the knee; this ligament keeps the knee from hyperextension or being displaced back from the femur. The ACL is a rather large ligament that can withstand 500 lb(227 kg) of pressure. If it is torn or becomes detached, it remains that way and surgery is indicated. In the most severe cases, a graft to the ligament is necessary to reattach it to the bone. The surgery can use tissue from the patient, called an autograft, or from a cadaver, called an allograft. The patella tendon, which connects the patella to the tibia, is the most commonly used autograft. ACL reconstructive surgery involves drilling

a tunnel into the tibia and the femur. The graft is then pushed through the tunnels and secured by stapling or sutures.

b. Posterior cruciate ligament (PCL): A back-crossing ligament that attaches the front of the femur to back of the tibia behind the knee that keeps the knee from hyperextension or being displaced backward. PCL injuries are not as frequent as ACL injuries. These injuries are largely due to falls directly on the knee or hitting the knee on the dashboard of a car in an accident. Both displace the tibia too far back and tear the ligament. Surgery to the PCL is rare, because the tear can usually be treated with rest and with rehabilitation. If surgery is required, it is usually to reattach the PCL to the tibia bone.
c. Medial collateral ligament (MCL): This is an inside lateral ligament connecting the femur and tibia and stabilizing the knee against lateral dislocation to the left or to the right. The injury is usually due to external pressure against the inside of the knee. In the case of a grade I or II collateral ligament tear, doctors are likely to brace the knee for four to six weeks. A grade III tear may require surgery to repair ligament tear and is followed by three months of bracing. Physical therapy may be necessary before resuming full activity.
d. Lateral collateral ligament (LCL): An outside lateral ligament connecting the femur and tibia and stabilizing the knee against lateral dislocation. In the case of a grade I or II collateral ligament tear, doctors are likely to brace the knee for four to six weeks. A Grade III tear may require surgery to reattach the ligament to bone. Surgery will be followed by three months of bracing. Physical therapy may be necessary before resuming full activity.

Patello-femoral syndrome (PFS):The patella rests in a groove on the femur. Anything but a good fit can cause the patella to be unstable in its movement and very painful. Some individuals have chronic problems with the proper tracking of the patella with the femur. This may be associated with conditions related to physical features like foot pronation, or to types of body development in exercizing or overuse of muscles. In the case of damage, an examination of the cartilage surrounding the patella can identify cartilage that increases friction as the patella moves. Smoothing the damaged cartilage can increase the ease of movement and eliminate pain. Finally, a tendon can occasionally make the patella track off center of the femur. By moving where the tendon is attached through lateral release surgery, the patella can be forced back into its groove.

Disease and injury can damage joints, ligaments, cartilage, and bone surfaces. Because the knee carries most of the weight of the body, this damage occurs almost inevitably as people age, due to sports injuries and through accidents.

Diagnosis and preparation: The diagnosis of knee injuries or damage includes: A medical history, physical examination, X-rays, and more detailed imaging techniques with MRI or CT scan. During the first visit by patient, the decision is made for surgery or for rehabilitation. Factors that influence the decision for surgery are: the likelihood for repair and recovery of function, the patient's health and age, and the willingness of the patient to consider changes in lifestyle. Arthroscopic viewing is the most accurate tool for diagnosis, as well as for some repairs. The surgeon may provide only a provisional diagnosis until the actual surgery but will apprise the patient of the most likely course

the surgery will take. Knee arthroscopic surgery can be performed under local, regional, or general anesthetic. The procedures are conducted through the visualization offered by the lighted arthroscope that allows the surgeon to follow the surgery on a television monitor. Instruments only about 0.15 in (4 mm) thick are inserted in a triangular fashion around the knee. The arthroscope goes in one incision, and instruments to cut and/or smooth and to engage in other maneuvers are put through the other incisions. In this fashion, the surgeon has magnification, perspective, and the ability to make tiny adjustments to the tissue without open surgery. The triangular approach is highly effective and safe. After the procedure, the incisions are closed, the leg is wrapped tightly and the patient is taken to the recovery room. For most same-day surgeries, individuals are allowed to leave once the anesthetic effects have worn off. Patients are advised not to drive. Arrangements for pick up after surgery are mandated. Follow-up visits are scheduled within about a week, at which point dressings are removed.

11.3.2.2 PAIN MANAGEMENT

Pain management surgeries are used to relieve severe discomfort of the knee due to osteoarthritis conditions. The objectives of treatments include: Relief from the pain and instability caused by more chronic, "wear and tear" kinds of conditions; consideration of an optional surgical procedure to treat cartilage and bone surfaces. These include arthroscopic techniques to remove the detached or obtruding pieces of cartilage in the joint space such as the meniscus (a fibrous cushion for the patella), to smooth aged, rough surface bone, or to remove parts of the lining of the inflamed joint.

Surgery indications for pain management are largely for chronic damage and for the milder grades or stages of acute injuries (severity Grade I and II). These are controversial due to the existence of pain management and rehabilitation alternatives.

PAIN MANAGEMENT WITH LAVAGE AND DEBRIDEMENT

In addition to the ligament and patella surgeries that are largely required for traumatic injuries, arthroscopic surgery treats the wear and tear injuries related to a torn meniscus, which is the crescent-shaped cartilage that cushions the knee, as well as injuries to the surface of bone that makes joint movement painful. These are related to osteoarthritis and rheumatoid arthritis.

In lavage and debridement, the surgeon identifies floating or displaced tissue pieces and either flushes them out with a solution applied with arthroscopy or smoothes the surface of bone to decrease pain.

11.3.2.3 AFTERCARE

Ligament- and patella-tracking surgeries: Arthroscopic surgery for severe ligament damage or knee displacement often involves ligament grafting. In some cases, this includes taking tissue from a tendon to use for the graft and drilling holes in the femur or tibia or both. **Aftercare** involves the use of crutches for six to eight weeks. A rehabilitation program for strengthening is usually suggested. Recovery times for resumed athletic activity are highly dependent on age and health. The surgeon often makes very careful assessments about recovery and the need for rehabilitation. Patella-tracking surgeries offer about a 90% chance that the patella will no longer dislocate. However, many people can continue to have swelling and pain after surgery. These seem to be dependent upon how carefully the rehabilitation plan is developed and/or adhered to by the patient.

Lavage and debridement surgeries:Elevation of the leg after surgery is usually required for a short period. A crutch or knee immobilizer adds additional stability and assurance when walking. Physical therapy is usually recommended to strengthen the muscles around the knee and to provide extra support. Special attention should be paid to any changes to the leg a few days after surgery. Swelling and pain to the leg can mean a blood clot has been dislodged. If this occurs, the physician should be notified immediately. Getting out of bed shortly after surgery decreases the risk of blood clots.

11.3.2.4 NORMAL RESULTS

Normal results of ligament surgery are pain, initial immobility and inflexibility, bracing of the leg, crutch dependence, with increasing mobility and flexibility with rehabilitation. Full recovery to the level of prior physical activity can take up to three months. With ACL surgery, pain in the front of the knee occurs in 10–20% of individuals. Limited range of motion occurs in less than 5% due to inadequate placement of the graft. A second surgery may be necessary.

Research indicates that the pain-relieving effects for arthroscopic partial menisectomy(removal of torn parts of cartilage) and debridement (the abrasion of cartilage to make it smooth) are not very reliable. Pain relief varies between 50% and 75%, depending upon the age, activity level, degree of damage, and extent of follow-up. Debates about normal expectations from minor arthroscopic surgery continue among many surgeons believing that arthroscopic surgery of the knee should be restricted to acute injuries.

11.3.2.5 MORBIDITY AND MORTALITY RATES

Complications occur in less than 1% of arthroscopic surgeries. Different procedures have different complications. In general, morbidity results mostly from medically induced nerve and vascular damage; death or amputations almost never occur. Graft infection may occur, along with other types of infection largely due to microbes introduced with instruments. The latter cases are becoming increasingly rare as the science of arthroscopic surgery develops.

11.3.2.6 ALTERNATIVES

Whether or not surgical treatment is the best choice depends on a number of factors and alternatives. Age and the degree of injury or damage are important considerations to decide whether to have surgery or rehabilitation. The physician evaluates the severity of acute injuries and either proceeds to a determined treatment plan immediately or recommends surgery. Alternatives for acute ligament injuries depend on the severity of injury and whether the patient can make lifestyle changes and is willing to move away from athletic activities. This decision becomes paramount for many people with collateral and cruciate injuries.

According to the American Association of Orthopedic Surgeons(AAOS), conservative treatment for acute injuries involves **RICE: Rest, Ice, Compression, Elevation**, as well as a follow-up rehabilitation plan. The RICE protocol involves resting the knee to allow the ligament to heal, applying ice two or three times a day for 15–20 min, compression with a bandage or brace, and elevation of the knee whenever possible. Rehabilitation requires range-of-motion exercises to increase flexibility, braces to control joint immobility, exercise for quadriceps to support the front of the thigh,

and upper thigh exercise with a bicycle.For arthritis-related damage and pain management, antiinflammatory medication, weight loss, and exercise can all be crucial to strengthening the knee to relieve pain. Evidence suggests that these alternatives work as well as surgery.

11.3.3 MENISCUS SURGERY

There are three types of surgery for torn meniscus: Partial meniscectomy, meniscus repair, and complete meniscectomy.Today, almost all types of meniscus surgeries are done arthroscopically. In arthroscopic surgery, small incisions are made and a flexible tube with a miniature camera and light source attached is inserted. The procedure is guided by images from the camera. Tiny instruments are placed at the tip of the tube to perform the surgical procedure(Fig. 1).

Partial meniscectomy(removal of torn meniscus tissue):Since the meniscus serves an important function in the knee, it is best to save as much of the meniscus as possible. A partial meniscectomy involves the removal of the torn piece of the meniscus only and the undamaged portion of the meniscus remains in place. This procedure is typically performed arthroscopically.A small shaver is used to remove the torn part of the meniscus.This is different than a surgery for meniscus repair.

Meniscus repair involves suturing together the torn portions of the meniscus and allowing the meniscus to heal. Meniscus repair is far less common than partial meniscectomy because a repair can only be done if the tear is in the area of the meniscus that has a blood supply (the outer edge or “red zone”). Other factors can also limit the success of this procedure. For example, complex tears or tears in cartilage that is very worn or thin are less likely to respond well. In a repair procedure, the surgeon will use either sutures or small bio-absorbable tacks to bring the pieces of meniscus back together.

Complete meniscectomy is the complete removal of the meniscus. In the past, this used to be a common procedure; but today it is avoided, if possible. The absence of the meniscus often leads to bone-on-bone friction, resulting in arthritis.Some physicians believe there is an open issue about whether partial meniscectomy causes or accelerates arthritis.

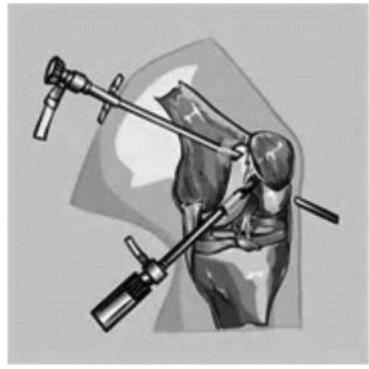

FIGURE 1 Meniscus surgery

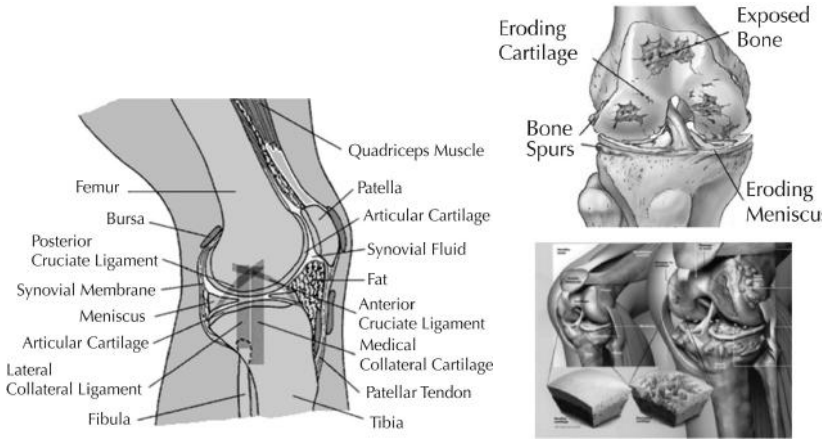

FIGURE 2 Left: Knee joint ligaments; Right: Osteoarthritic Knee.

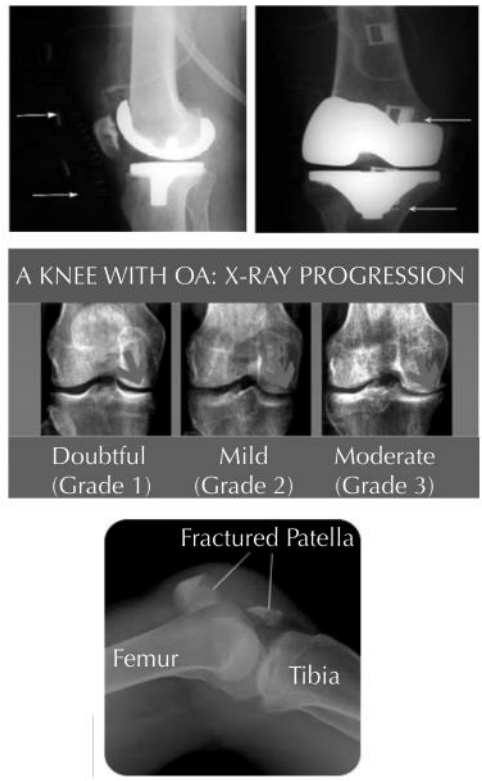

FIGURE 3 X-ray of the injured knee.

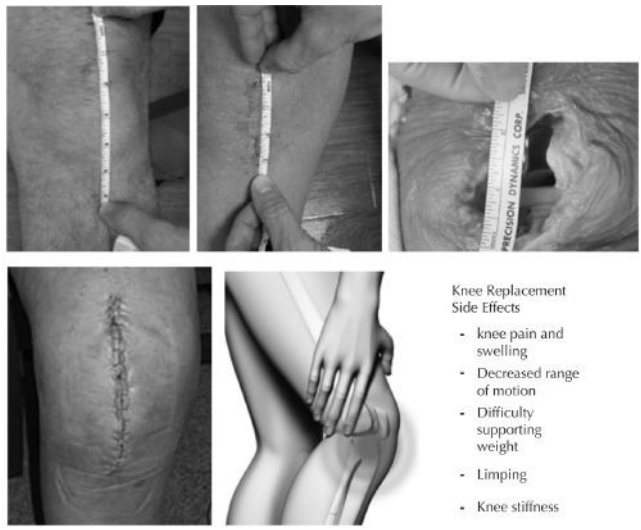

FIGURE 4 The incision for total knee implant surgery (A, B, C); the incision after surgery (D); and possible side effects (E).

11.4 RESEARCH ADVANCES

Total knee replacement (TKR) has been practiced for over 50 years. The complexities of the knee joint only began to be understood 30 years ago. Because of this, total knee replacement initially was not as successful as Sir John Charnley's artificial hip. However, over the last 20 years, dramatic advancements in the knowledge of knee mechanics have led to design modifications that appear to be durable. Significant advances have occurred in the type and quality of the metals, polyethylene, and more recently, ceramics for the prosthesis manufacturing process.Knee joint ligaments and osteoarthritic knee are shown in Figs. 2 and 3. The possible incisions for total knee implant surgery are shown in Fig. 4. Figures 5 to 6 indicate a typical TKR. All this led to improved longevity. Since the beginning of the modern era of total joint arthroplasty(TJA), the materials used to manufacture implants for total knee (TKA) and total hip (THA)arthroplasty, were originally developed for unrelated applications. Generally, these materials are cobalt chromium, ceramics, titanium alloy and ultra high molecular weight polyethylene (UHMWPE).

Oxinium technology is the culmination of longtermefforts by Smith and Nephew and it successfully combines the best features of cobalt chromium (strength) and ceramic (scratch resistance) into one unique material that has been specifically developed for TJA to be used as a bearing surface. Oxinium implants are manufactured from metallic alloy (Zirconium and Niobium) forgings that undergo controlled and forced oxidation processes. The oxidation process transforms the surface of the implant into zirconia ceramic.

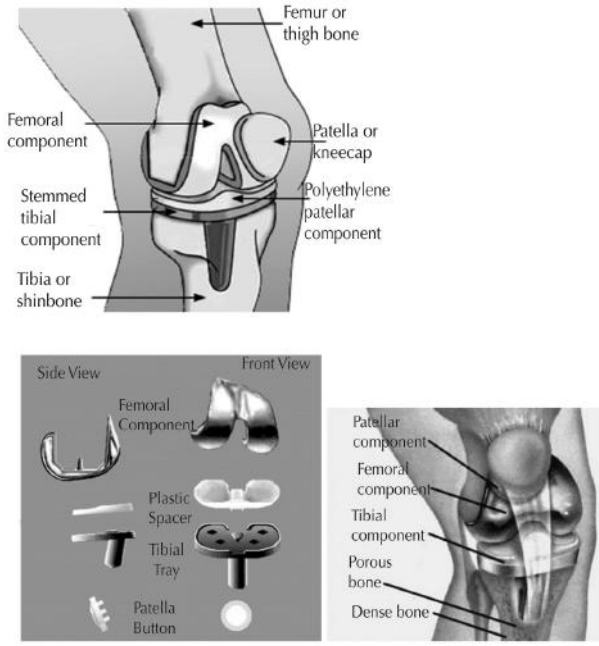

FIGURE 5 An example of "Total Knee Replacement Prosthesis" with components (MMG, Inc.).

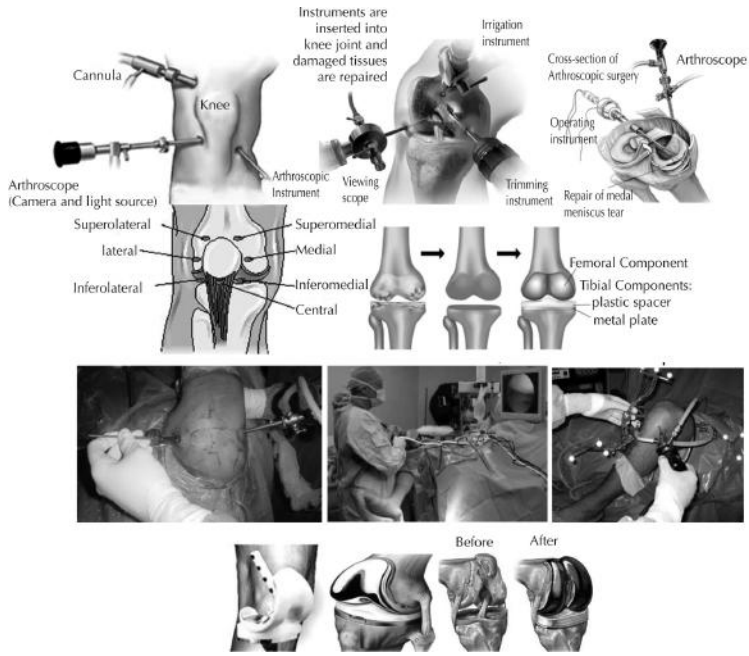

FIGURE 6 Total knee replacement procedure.

Implant components manufactured from Oxinium technology have undergone significant laboratory testing and have been shown to be 4900 times more scratch or abrasion resistant than cobalt chromium, 220% harder than cobalt chromium, and superior to cobalt chromium in fatigue strength. In addition, these components have demonstrated an 85% reduction in the UHMWPE wear generation when compared to cobalt chromium components of the same design.

A new minimally invasive technique called unicondylar knee replacement is helping the 30 to 40 percent of patients with unicompartmental arthritis. The technique replaces only the affected segment of the knee. A metal runner and small plastic disc replace the worn cartilage, providing a new cushion between the bones. Though originally developed in the 1970s, yet the technique has been improved as a result of advances in materials and technique.

11.5 SCOPE OF THE BIOMATERIALS

In all fields of engineering, designers/manufacturers/and end users are looking for improved performance of products and processes.Relevant information is needed for alloys with: higher strength, superior corrosion resistance and other desirable combinations of properties.Titanium is regularly supplied by a large number of manufacturers. Titanium is not an “exotic” metal.It is the fourth most abundant structural metal in the earth’s crust and is the ninth industrial metal. No other engineering metal has risen so swiftly to preeminence in critical and demanding applications. Titanium and its alloys have proven to be technically superior and cost-effective in a wide variety of aerospace, industrial, marine, medical and commercial applications. In the majority of bioengineering applications, titanium has replaced heavier, less serviceable or less cost effective materials.

Designing with titanium, taking all factors into account has resulted in reliable, economic, and more durable systems and components, which in many situations have substantially exceeded performance and service life expectations. Titanium does not exhibit a toxic property and its adaptability to implants for human body is an added advantage.

Although Titanium is an acceptable biomaterial, yet Oxinium is a new biomaterial in the market for TKR applications. This material is as strong as the Titanium.Oxiniumconjuction with Polyethylene, make an acceptable combination providing minimal wear.Even though Aluminum Oxide and Chromium Alloys have been used in the past, it seems that the future of the TKR rellies on three materials: Titanium, Oxinium and Ultra High Molecular Weight Polyethylene (UHMWP). It consists of titanium alloy at the upper and lower structural components. A zirconia wear surface has been fabricated for the upper section. Similar to the hip prosthesis, this articulates against a UHMWPE insert on the lower section. The abrasive resistance of Oxinium and Cobalt – Chrome alloy is compared in Fig. 7.

11.6 DESIGN REQUIREMENTS

11.6.1 TITANIUM

Light, strong and totally biocompatible, titanium is one of few materials that naturally match the requirements for implantation in the humanbody. Titanium and some of its

alloys are used as biomaterials for orthopedic applications. The most common grades used are commercially pure titanium and the Ti_6Al_4V alloy. Some designs, including cementless joints, use roughened bioactive surfaces (including hydroxyapatite) to stimulate osseointegration, limit resorption and thus increase the implant lifetime for younger recipients. The surface of titanium is often modified by coating it with hydroxyapatite. The hydroxyapatite provides a bioactive surface (i.e., it actively participates in bone bonding), so that bone cements and other mechanical fixation devices are often not required.Plasma spraying is the only commercially accepted technique for depositing such coatings. Characteristics of Titanium alloys in joint replacements surgery are:

- Most common combination is Ti_6Al_4V.
- Strong and corrosion resistant.
- Young's modulus of elasticity of 110 GPa (less than cobalt chrome and stainless steel), therefore often used for cementless joint replacements.
- Poorer wear characteristics.
- Ultimate Strength: Stainless Steel > Titanium;Yield Strength (permanent deformation): Titanium > Stainless Steel.
- $Ti_{13}Zr_{13}Nb$ is stronger and has lower Young's modulus.

Theoretically, it may promote bone apposition and bone ingrowth more than cobalt chrome, but no difference has been found clinically.

11.6.2 ALUMINUM OXIDE OR ALUMINA

Aluminium oxide(Al_2O_3) is also called alumina. Aluminium oxide is the main component of the principal ore of aluminum(bauxite), and the main component of gems, such as: ruby and sapphire.Metallic aluminum is very reactive with atmospheric oxygen, and a thin layer of aluminum oxide quickly forms on any exposed aluminum surface during the weathering process. This layer protects the metal from further oxidation. Powdered aluminum oxide is frequently used as a medium for chromatography.Other applications for alumina encompass porous coatings for femoral stems, porous alumina spacers (specifically in revision surgery), knee/hip prostheses and as polycrystalline/single crystal forms for dental implants.

In knee simulator tests, UHMWPE wear against alumina decreased to 1/10 of that against metal. Clinically no revisions were carried out due to the polyethylene wear problems during the past 23 years. In retrieved cases, UHMWPE surface against alumina is very smooth However in a comparative study on UHMWPE surface against metal, many fibrils and scratches have been reported, showing extremely good performance of alumina ceramics against UHMWPE.

11.6.3 OXINIUM

In the past, orthopedic surgeons used to advise patients under the age of 65 to wait to have joint replacement surgery because the life span of traditional implants was limited.The younger patients desire to return to an active lifestyle that may include low demand sports, dancing, gardening, and other activities.With Oxinium implants, these younger patients can benefit from the replacements.The Oxinium material demonstrates low wear rates and can tolerate the daily activities. The biocompatibility of the

Oxinium material has been confirmed by testing in accordance with ASTM and ISO standards, as indicated below:

1. Cytotoxicity (L929 MEM Fibrolast).
2. Sensitization (Kligman Maximization).
3. Genotoxicity(Ames Mutagenicity and Micronucleus Assay).
4. Implantation (90-Day Intramuscular and 6-Month Transcortical).
5. Intracutaneous Reactivity (Intracutaneous Injection).
6. Acute Toxicity (Systemic Injection and Pyrogenicity).
7. Haemocompatibility(Hemolysis): Oxinium is at least as biocompatible as cobalt chrome and titanium alloys.

<http://www.smith-nephew.com/> indicates that "Oxinium oxidized zirconium is available for the knee implant systems.It is a superior choice for hip and knee implants due tocombination of hardness, smoothness and scratch-resistance prperties. Oxiniumwith the surface transformed to ceramic using a patented process has proven to be a superior biomaterial for use in hip and knee implants due to its reduced friction and increased resistance to scratching and abrasion. These superior properties result in significantly less wear than can be produced by cobalt-chrome alloy. Some noteworthy propties of Oxinium are: 1. It has a surface hardness that is over twice that of cobalt-chrome. It may last longer than other implants as it reduces more than half of the implant wear common to other knees and hipsbased on lab simulator studies;2.It avoids the risk of brittle fracture that can occur with ceramic implants. It is20% lighter than cobalt-chrome; and 3. It contains no detectable nickel, the leading cause of negative reactions in patients with metal allergies."

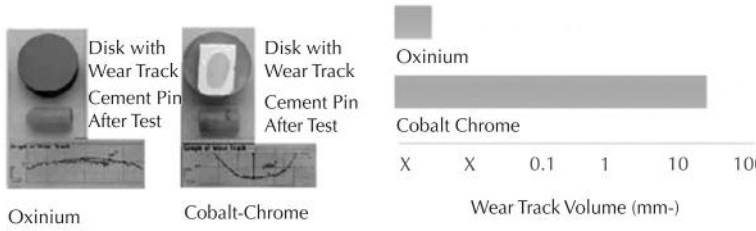

FIGURE 7 Abrasion amount (per mm) for oxinium and cobalt chrome.<http://www.oxinium.co.uk/surgeons/abrasion_resistance.php>.

11.6.4 ULTRA HIGH MOLECULAR WEIGHT POLYETHYLENE (UHMWPE)

Polyethylene (PE) is most popular plastic in the world. The PE is a vinyl polymer, made from the monomer ethylene. A molecule of polyethylene is a long chain of carbon atoms, with two hydrogen atoms attached to each carbon atom. Sometimes some of the carbons, instead of having hydrogens attached to them, will have long chains of polyethylene attached to them. This is called branchedor low-density polyethylene (LDPE). When there is no branching, it is called linear polyethylene (HDPE). HDPE is much stronger than LDPE that is cheaper and easier to make.HDPE is normally produced with molecular weights in the range of 200,000 to 500,000.The PE with

molecular weights of three to 6 millions is referred to as ultra-high molecular weight polyethylene (UHMWPE).The UHMWPE is used to make fibersinto large.Depending on the processing of the material, PE can be elastic and flexible, or hard and smooth.

The "artificial joint or prosthesis" generally has two components, one made of metal alloy. The other component is a UHMWPE.The LDPE serves as tubing in catheters, while UHMWPE is one of the major articulating surfaces used in total hip or knee replacements.The smooth surface of UHMWPE creates low friction with other biomaterials and increases the durability of the artificial joint exponentially.

11.7 FUNCTIONAL REQUIREMENTS OF BIOMATERIALS

11.7.1 TITANIUM

The natural selection of titanium for implantation is determined by a combination of most favorable characteristics including immunity to corrosion, biocompatibility, strength, low modulus and density, the capacity for joining with bone and other tissue – osseointegration. Osseointegrated titanium implants meeting all the requirements of bio-compatibility and strength have made possible unprecedented advances in surgery.'Fit and forget' is an essential requirement where equipment in critical applications, once installed, cannot readily be maintained or replaced. Here, the effectiveness and reliability of implants, and medical and surgical instruments and devices are essential factors for the long-term relief from suffering and pain.

Most metals in body fluids and tissue are found in stable organic complexes. Corrosion of implanted metal by body fluids, results in the release of unwanted metallic ions, with likely interference in the normal life. Corrosion resistance is not sufficient to suppress the reaction of body to cell toxic metals or allergenic elements and even in very small concentrations from a minimum level of corrosion.These may initiate rejection reactions. Titanium is considered as bioinert and immune to corrosion by all body fluids and tissue, andtherefore is bio-compatible.Titanium and its alloys are classified as biologically inert biomaterials or bioinert.It imples that they remain essentially unchanged when implanted into human body. The human body recognizes these materials as foreign, and tries to isolate them by encasing them in fibrous tissues. However, they do not illicit any adverse reactions and are tolerated well by the human body. Furthermore, they do not induce allergic reactions such as has been observed with some stainless steel biomaterials that have induced nickel hypersensitivity in surrounding tissues.

11.7.2 ALUMINUM OXIDE

Alumina currently is used for orthopedic and dental implants, andcan be polished to a high surface finish and high hardness. It has been utilized in wear bearing environments such as the total hip arthroplasties(THA), as the femoral head generating reductions in wear particles from ultrahigh molecular weight polyethylene (UHMWPE).

High purity alumina bioceramics have been developed as an alternative to surgical metal alloys for total knee prosthesis and tooth implants. The high hardness, low friction coefficient and excellent corrosion resistance of alumina offers a very low wear rate at the articulating surfaces in orthopedic applications. Medical grade alumina has a very low concentration of sintering additives (<0.5% by weight), very small grain

size (<7 μm) and a narrow grain size distribution. Such a microstructure is capable of inhibiting static fatigue and slow crack growth while the ceramic is under load. The average grain size of current medical grade aluminas is 1.4 μm.The surface finish is usually controlled to a roughness of less than 0.02 μm. However, unless its surface modified or used directly in articulating areas, alumina has a fundamental limitation as an implant material, because a nonadherent fibrous membrane may develop at the interface. In certain circumstances, interfacial failure can occur, leading to loosening, as has been observed in some earlier dental implants.

Diffusion bonding is a solid phase process achieved via atomic migration with no macrodeformation of the components. Initial surface flatness and cleanliness are essential. Surface roughness values of less than 0.4 microns are required and the samples must be cleaned in acetone prior to bonding. Typically the process variables range from several hours at moderate temperatures ($0.6*T_m$) to minutes at higher temperatures ($0.8*T_m$), with applied pressure. The process can be used for diffusion bonding to itself and to metals.Ceramic-ceramic diffusion bonding is difficult to achieve unless either diffusion aids or (more commonly) secondary phases are present. These are most typically glassy phases at grain boundaries.

Bonding of thin films to build up complex 3-D structures is one of the most up-to-date applications for this technology. This has been achieved for rapid prototyping of alumina components. Some may argue that this is sintering; and in reality there is little difference in the mechanics of diffusion bonding and sintering.

When joining dissimilar materials, there is usually an added complicationdue to-differences in coefficient of thermal expansion (CTE). This can developthermal strains at the interface which can cause premature failure of the bond. This can be overcome by ensuring correct design of the bond line and/or by using interlayers, which have CTE's intermediate to those of the materials to be joined and often have a low elastic modulus. Appropriate stacking of interlayers (ranging in thickness from microns to millimeters) can allow diffusion bonding to take place.

11.7.3 OXINIUM

Zirconium alloy metal is shaped into an implant component.The implant is put through a patented process that allows oxygen to be absorbed by the zirconium metal.When the metal is saturated with oxygen, it changes from a metal to a ceramic. It is the ceramic surface that gives the material the significant advantage over cobalt chrome alloy. Only the surface is changed, the rest of the component is metal, regaining its overall strength. It combines the best features of cobalt chromium (strength) and ceramic (scratch resistance) into one unique material that has been specifically developed for TJA to be used as a bearing surface.

The ceramic surface of Oxinium makes implants 4,900 times more abrasion resistant than cobalt chrome (Fig. 7).The material's surface is considerably harder and much more resistant to scratches.Because the implant is metal, there is no risk of fracture – a problem seen with ceramic hip implants.The result is superior durability over time and longievity.Oxinium material is a choice in knee and hip replacement materials for patients who exhibit metal allergies.It contains no detectable nickel, the leading cause of negative reactions in patients with metal allergies.

11.7.4 ULTRA HIGH MOLECULAR WEIGHT POLYETHYLENE (UHMWPE)

Much research is progressing in examining the wear properties of UHMWPE.The coefficient of friction between polyethylene and cobalt-chromium alloy (commonly used for femoral components) has been reported to be between 0.03 and 0.16, with excellent wear rates. The shape and congruency of the bearing surface is important with respect to contact of the metal component on the polyethylene.

The mobile bearing insert (compared to a fixed bearing) is constantly being researched with the focus directed to the contact of these surfaces, such that it aims at achieving low contact stresses to decrease wear and further increase range of movement. There is much more area of contact in the mobile bearing systems. This is a disadvantage, as there is more area to wear. Mobile bearings have significantly reduced upper and lower surface stresses compared with fixed-bearing components. Unconstrained mobile bearings have a theoretical advantage compared to semiconstrained mobile bearings (which allow rotation or translation), as they avoid higher shear stresses, but they also have an increased risk of subluxation. Low friction is the aim in the design of all prostheses. Therefore, opportunities for improvement exist in developing finer polishing techniques and better interface materials.

Major long-term problems that are associated with total knee arthroplasty are late infection, wearing of the bearings, and loosening of the prosthesis. Periprosthetic fracture and arthrofibrosis are other problems that may occur but are less common. Osteolysis is a major problem with polyethylene and metal wear fragments. The pathology consists of a significant synovitis caused by the presence of the wear particles in the synovial cavity. Due to the Pascal principle, major forces are produced and transmitted throughout the synovial fluid. These particles are forced along the lines of least resistance, and the inflamed synovium tracks down the vascular bony foramina around the joint. Severe osteolysis can also occur in pigmented villonodularsynovitis and in patients with hemophilia.

11.8 MECHANICAL PROPERTIES OF BIOMATERIALS

11.8.1 TITANIUM

The mechanical and physical properties of titanium alloys make the implants highly damage tolerant. The human anatomy naturally limits the shape and allowable volume of implants. The lower modulus of titanium alloys compared to steel is a positive factor in reducing bone resorbtion. Two further parameters define the usefulness of the implantable alloy: the notch sensitivity, and the resistance to crack propagation, or fracture toughness. Titanium scores well in both cases. Typical NS/TS ratio for titanium and its alloys varies from 1.4 to 1.7 (1.1 is a minimum for an acceptable implant material). Fracture toughness of all high strength implantable alloys is 50 MPa-$m^{-0.5}$ with critical crack lengths well above theminimum for detection by standard methods of nondestructive testing. Medical grade titanium alloys have a significantly higher strength to weight ratio than competing stainless steels. The range of available titanium alloys enables medical specialists and designers to select materials and forms closely tailored to the needs of the application. The full range of alloys reaches from high ductility commercially pure titanium used where extreme formability is essential, to fully heat treatable alloys with strength above 1300 MPa(190 ksi).

Shape–memory alloys based on titanium further extend the range of useful properties and applications. A combination of forging or casting, machining and fabrication are

the process routes used for medical products. Surface engineering frequently plays a significant role, extending the performance of titanium several times beyond its natural capability. Forms and material specifications are detailed in a number of international and domestic specifications, including ASTM and BS7252/ISO 5832. Other specific properties that make it a desirable biomaterial are density and elastic modulus. In terms of density, it has a significantly lower density (Table 1) than other metallic biomaterials, meaning that the implants will be lighter than similar items fabricated out of stainless steel or cobalt chrome alloys. Having a lower elastic modulus compared to the other metals is desirable as the metal tends to behave a little bit more like bone itself, which is desirable from a biomechanical perspective. This property means that the bone hosting the biomaterial is less likely to atrophy and resorb. Titanium and its alloys offer:

- Availability in all forms.
- Comparable cost to other high performance materials.
- Ready weldability and machinability.
- Weight saving – as strong as steel, but half the weight.
- Fire and shock resistant.
- Favorable cryogenic properties.
- Biocompatibility and nontoxicity.
- Excellent resistance to corrosion.
- Young's modulus approximately half that of stainless steel, therefore less risk of stress protection of bone, stress riser at end of plate or nail.
- More expensive than stainless steels.
- Can be brittle i.e., less ductile than stainless steel, but more ductile titanium alloys being produced.

TABLE 1 Density and elastic modulus of selected biomaterials and cortial bone.

Material	**Density,** g.cm-^{3}	**Elastic Modulus, GPA**
Cortical Bone	~2.0	7–30
Cobalt-Chrome alloy	~8.5	230
316L Stainless Steel	8.0	200
CP Titanium	4.51	110
Ti-6Al-4 V	4.40	106

TABLE 2 Properties of Alumina ceramics at 20°C.

Property	**Units**	**960P**	**975P**	**995P**	**96S**	**ZTA**
Al_2O_3	%	96.0	97.5	99.7	96.0	80.0
Bulk Density	g/cm^3	3.67	3.75	3.96	3.77	4.1
Tensile Strength	MPa	205	205	220	—	—
Flexural (Bending) Strength	>MPa	375	375	410	295	450
Elastic Modulus	GPa	300	355	375	—	340
Hardness	kg/mm^2	10	12	14	—	16
Fracture Toughness	MPa$_*$m$^{1/2}$	4–5	4–5	4–5	–	7

11.8.2 ALUMINUM OXIDE

Alumina (Aluminum Oxide, Al_2O_3)is the most versatile ceramic because of its high temperature service limit along with its chemical, electrical and mechanical properties. It is relatively low cost, is easily formed and finished. It is often compounded with silica or trace elements to enhance its properties or fabrication and commonly will range from 92% to 99.8% of Al_2O_3. Although the final properties of alumina ceramics will be determined by the manufacturing method, they generally will have the following properties(Table 2):

- Strong ionic bonds between the metallic and nonmetallic components.
- Very strong and stiff.
- Biocompatible.
- Very hard, therefore good wear characteristics, but very brittle.
- Difficult to process due to very high melting points.
- Bioinert: Alumina and Zirconia are used for surface replacement.
- Bioactive: Hydroxyapatite and glass are used for coating joint replacements for osseous integration between bone and implant.
- Ceramic components for electrical insulation or isolation.
- Hermetic ceramic-to-metal seals for use in high vacuum applications.
- Custom ceramic components produced to extreme tolerances.
- Excellent wear and corrosion resistance.
- High and low-temperature glazing.
- Lapping (flat and cylindrical surfaces).
- High-purity: 95% to 99.9% of Al_2O_3.

11.8.3 STAINLESS STEEL

The stainless steel(SS) has a unique advantage. The chromium in the SS has a great affinity for oxygen, and will form on the surface of the steel at a molecular level a film of chromium oxide that can be about 130 Angstroms(0.10 nanometers = 1.0 Angstrom) in thickness. Stainless steels have good strength and good resistance to corrosion and oxidation at elevated temperatures.Characteristics of SS are summarized as:

- Iron based alloy containing chromium, nickel, molybdenum: Usually annealed, cold worked or cold forged for increased strength. A range of strength and ductilities can be produced.
- Strong and cheap.
- Relatively ductiletherefore easy to alter shape. Useful in contouring of plates and wires during operative procedures.
- Relatively biocompatible.
- The chromium forms an oxide layer when dipped in nitric acid to reduce corrosion and the molybdenum increases this protection when compared to other steels.
- Can undergo corrosion if carbon gets to the surface.
- High Young's modulus of 200 GPa(10' that of bone), so it can lead to stress shielding of surrounding bone that can cause bone resorption.
- Used in plates, screws, external fixators, I.M.nails.

- Composition of 316L Stainless Steel: Iron- 60%, Chromium- 20% (major corrosion protection), Nickel- 14% (corrosion resistance), Molybdenum- 3% (protects against pitting corrosion), Carbon- 0.03% (incr. strength), Manganese, Silicon,P,S, — 3% (control manufacturing problems).
- Because of high Young's modulus, SS may be inserted with polymer cement of a a lower modulus: For fixation to prevent stress shielding of the surrounding bone.

11.8.4 OXINIUM(<HTTP://WWW.OXINIUM.CO.UK/NEWS/INDEX.PHP>)

Maximum Nickel content in Oxinium, Titanium and Cobalt – Chrome alloy is indicated in Fig. 8. The maximum nickel content for cobalt chrome can be as high as 1% compared to 0.1% for titanium alloy. The nickel content of Oxinium components cannot be detected. Surface hardness is correlated with abrasion resistance and stiffness. Using a "nano-hardness" technique, the relative hardness of the Oxinium material and cobalt chrome is compared in Fig. 9.For Oxinium femoral component, the effect of depth from surface on the surface hardeness is shown in Fig. 10for three zones: Ceramic oxide surface, oxygen enriched metal and metal substrate.

Cross-sectional profiles of the Oxinium material indicate a hard ceramic surface with a gradual decrease in hardness with distance from the ceramic(Fig. 10). This transition zone is an oxygen-enriched metal. The higher surface hardness of Oxinium components, coupled with a strong bonding between the surface ceramic oxide and the metal substrate, help explain the superior abrasion resistance of this material as compared to cobalt chrome.

Oxinium oxidized zirconium is a metallic alloy with a ceramic surface that provides wear resistance without brittleness.

Oxiniummaterial combines the best of both metal and ceramics. It is a metal, with excellent fracture toughness like cobalt chrome, but it has a ceramic surface that offers outstanding wear resistance:

- The ceramic is an enhanced surface that is part of the metal substrate rather than an external coating, making it very durable with unusual damage tolerance.
- Zirconium: a biocompatible metallic element in the same family as Titanium.
- Zirconia: a ceramic compound, wear-resistant but brittle.
- Zr-2.5Nb: a metallic alloy of zirconium, with niobium and oxygen for increased strength.

ASTM standards require implants to withstand loads that would normally be characterized as extreme. This test can simulate worst-case physiological conditions.Wear simulator test (Fig. 11) indicate thatthe Oxinium components are able to support a minimum fatigue load of 1,000 lbs. for 10 million cycles, which is equivalent to a cobalt chrome femoral component of the same design.The test shows the metal-like fatigue strength and toughness of the Oxinium component, unlike ceramic component that could shatter under these conditions.The UHMWPE wear debris particle is compared for Cobalt – Chrome alloy and Oxinium in Fig. 11.

11.8.5 ULTRA HIGH MOLECULAR WEIGHT POLYETHYLENE (UHMWPE)

In a TKR or TKA, mostly two materials are used: a plastic and a metal.For the plastic part of the replacement, Polyethylene is used. UHMWPE is used in almost every intervention with any part in the human body.Physical properties of this material include:environmental stress cracking resistance, outstanding wear and abrasion resistance, very low coefficient of friction, excellent toughness and impact resistance.

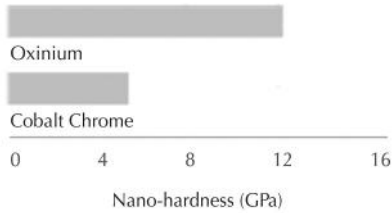

FIGURE 9 Surface hardness: Oxinium and Cobalt – Chrome alloy.

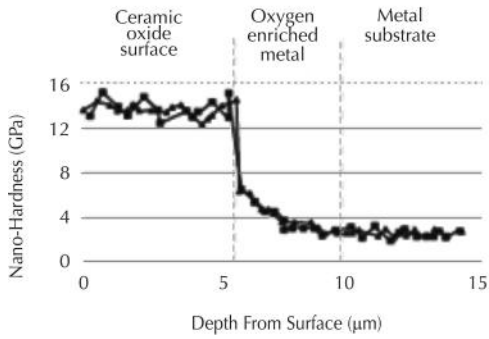

FIGURE 10 Oxinium profile: Effect of surface depth on hardness in three zones.

Although polyethylene is a plastic, it has advantages over metals like stainless steel.The plastic has a density of 0.94 g/cm^3 andSS has a density of 8.0 g/cm^3.The plastic has an elastic modulus of 600 and stainless steel of 200 GPa. Polyethylene is used in conjunction with another metal.They perform different functions in the arthroplasties, making it difficult to compare.The only bad outcome of this material is that with wear minuscule particles are spread because of the friction between the plastic and the metal in the TKR.

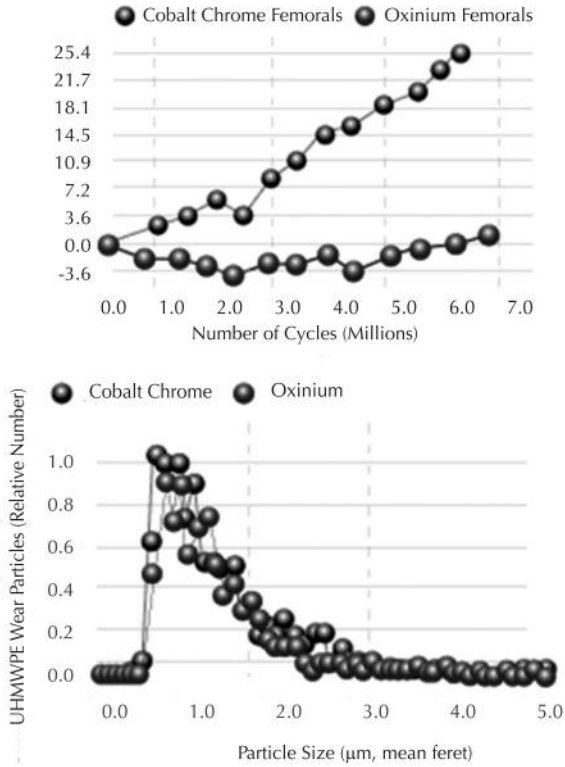

FIGURE 11 Left: Wear simulator test.Right: UHMWPE wear debris particle comparison for Cobalt – Chrome alloy and Oxinium.

11.9 CONCLUSIONS

Despite the increased success of "Total Knee Replacement," questions remain concerning which biomaterials and implant designs are most effective for specific patient population and which surgical approach is optimal for a successful outcome. Physical, social, and psychological issues may influence the success of TKR, and understanding patient differences can facilitate the decision-making processbefore, during, and after surgery, thereby achieving the greatest benefit from TKR. Particular attention also must be given to the treatment and timing options related for the revision of failed TKR surgery.

11.10 SUMMARY

In the past decades, the life expectancy of the population has increased substantially, a fact that has led to an increase in the prevalence of degenerative joint diseases. Hip, knee and shoulder replacement arthroplasties have been shown to be effective and to have predictable results in patients with osteoarthritis of these major joints. Knee replacement surgery is a medical procedure where a patient's full or partial knee structure

is replaced by synthetic components. It is designed to allow the patient to retain as much function as possible while relieving pain in the knee and surrounding areas. The majority of knee replacements are performed due to osteoarthritis but may also be used to treat other conditions and diseases. Following prosthetic replacement, most patients are able to increase their physical activity.However, many surgeons suggest limited activities to prevent loosening of the prosthetic components or excessive wear of the new joint materials, though no prospective studies have addressed the effect of sports upon long-term survival of the prostheses.In this chapter, we have discussed biomaterials for knee prothesis.

KEYWORDS

- **Abrasive wear**
- **Adhesive wear**
- **Alumina**
- **Aluminium oxide**
- **Anchor**
- **Arthroplastic surgery**
- **Arthroplasty**
- **Bioinert**
- **Biological system**
- **Biomaterial**
- **Bone loss**
- **Brittleness**
- **Calcium phosphate**
- **Calcium phosphate mineral**
- **Ceramics**
- **Corrosion**
- **Ductility**
- **Galvanic cell**
- **Genotoxicity**
- **Hydroxyapatite**
- **Knee prosthesis**
- **Modulus of Elasticity**
- **Necking**
- **Osseointegration**
- **Percentage elongation**
- **Proof stress**

- **Sensitization**
- **Skin**
- **Stiffness**
- **Strain**
- **Stress-strain graph**
- **Total joint replacement**
- **Total knee replacement**
- **Toughness**
- **Ultimate stress**
- **Yield Stress**
- **Young's Modulus**

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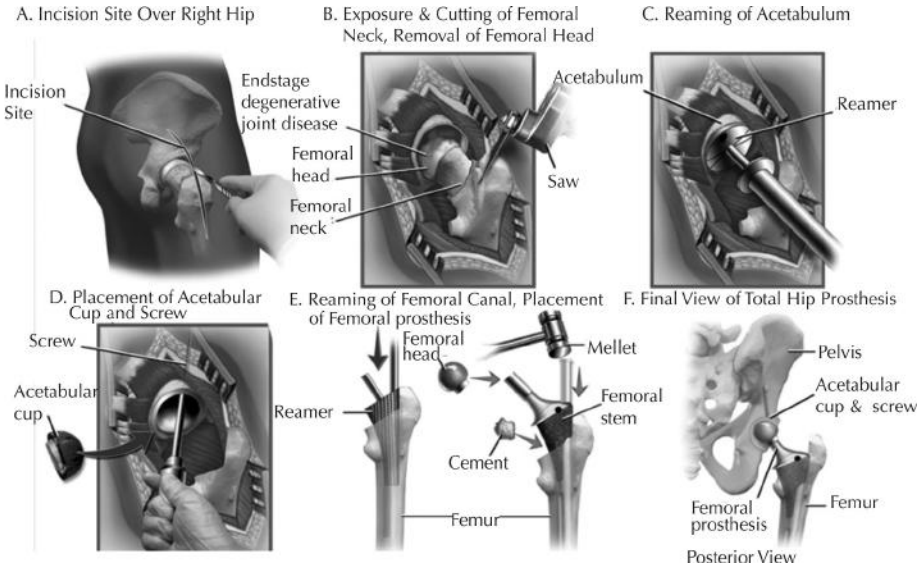
APPENDIX – AN EXAMPLE OF A TOTAL HIP REPLACEMENT



CHAPTER 12

BIOMECHANICS OF DENTAL PROSTHESES[1,2]

CONTENTS

[1]This chapter has been modified from the review article prepared by my students (Josué M. Arroyo, Josué M. Diaz, Angel M. Hernandez and Edwin Rodriguez) for the course on Mechanics of Materials – I, INGE 4011. Course Instructor: Megh R. Goyal, PhD, PE, Retired Professor in Biomedical Engineering, General Engineering Department, University of Puerto Rico – Mayaguez Campus, PO Box 86, Rincón, Puerto Rico 00677–0086. For details contact at <goyalmegh@gmail.com> or visit at: <http://www.ece.uprm.edu/~m_goyal/home.htm>. We acknowledge the cooperation and contribution by the faculty of Mechanical Engineering Department and Chemical Engineering Department at University of Puerto Rico – Mayaguez.
[2]The numbers in parentheses refer to cited references in the bibliography.

12.1 INTRODUCTION

One can loose a tooth due to dental diseases and conditions like: cavities and periodontal. The loss of one or more dental pieces contributes to a deficit in the mastication efficacy, with functionally and organic consequences. This is why patients prefer to replace dental pieces for dental prosthesis. Dental ontologists use a provisional prosthesis. The main purpose of using the provisional prosthesis is to restore the oral integrity of the patient until a final design of the prosthesis is elaborated. Although in some cases the maintenance of the prosthesis is secondary, this process is very important for the complete restoration of the set of teeth (Figs. 1 and 2). Hygienic precautions, correct use, maintenance and the conservation of the dental is a very important topic among patients, because cavities and other premalignant injuries can be avoided with use of established methods of maintenance. This chapter discusses biomechanics of dental prostheses and biomaterials for these prostheses.

12.2 HISTORICAL BACKGROUND

12.2.1 TREATMENT OF DENTAL AND PERIODONTAL DISEASES

— Papyrus records detail Egyptian remedies such as: stone powder, ocher (iron ore) and honey.
— Other civilizations developed plant remedies, including cloves, pepper, cinnamon, poppy seeds, ginger, copal (resin from trees), mint and tobacco.

12.2.2 DENTAL CARE

— Extraction was practiced by the Egyptians and in ancient Greece.
— Hippocratic literature devoted many paragraphs to dental care and included a numbering system for teeth.
— In Roman times, the Etruscans of central Italy made crowns and bridges, gold bands holding cadaver or calf teeth, or artificial teeth made from ivory or bone, though these soon rotted.
— Elizabeth I used cloth to fill the holes in her teeth to improve her appearance in public.
— A French pharmacist Duchateau and dentist Dubois de Chemant designed the first hard-baked, rot-proof porcelain dentures in 1774.
— The Englishman Claudius Ash invented an improved porcelain tooth around 1837.
— With Charles Goodyear's discovery of vulcanized rubber in 1839: A cheap, easily worked, moldable base for false teeth.
— With Horace Wells' discovery of nitrous oxide for painless teeth extraction in 1844, dentures became popular.

12.2.3 REMOVAL OF DECAY AND RESTORATION

— The oldest filling is >2,000 years old, being a piece of bronze wire inserted into the root canal of a Nabetan warrior in Egypt, believed to prevent 'tooth worms' being thought as the cause of decay well into the Middle Ages.
— In the Middle Ages: Resins, waxs and gums were used as fillings, with lead and gold introduced shortly after.

— The Frenchman Pierre Fauchard is considered the **father of modern dentistry**, developing an improved drill in 1728. He favored tin foil or lead cylinders for fillings.
— US dentist Robert Arthur developed the cohesive gold foil method in 1855.
— Amalgam (silver, or its alloys, combined with mercury) was developed by the Frenchman Auguste Taveau in 1816, with fears of leaky fillings and the effect of mercury on health surfacing quickly. These were not assuaged until the work of Chicago dentist G V Black in 1895 who standardized both cavity preparation and amalgam manufacture.

12.2.4 PREVENTION

— In ancient India and China medical writings recommended a toothbrush made from a frayed twig, and both tongue scrapers and toothpicks were in use.
— An American dentist trained his office assistant as a dental hygienist in 1906 and set up the first hygienist course in 1913 in Bridgeport – Connecticut, USA. This led to the first dental public health program.

12.2.5 HISTORY OF IMPLANTS

— 1940: Throughout history, we have seen an array of different sorts of materials used for dental devices. It was not until the latter part of the twentieth century, when materials such as porcelain, gutta percha and platinum were used. In the 1940s, Formiggini developed a screw type implant.
— 1952: With the advent of osseointegration, however, rootform endosteal implants became the new standard in implant technology. Brånemark's serendipitous discovery of osseointegration occurred in 1952 during vital microscopy studies in rabbits using titanium optic chambers.

He and his team found that titanium oculars placed into the lower leg bones of rabbits could not be removed from the bones after a period of healing. He then developed and tested a type of dental implant using pure titanium screws, which he termed fixtures. Brånemark's discovery of osseointegration revolutionized the realm of implant dentistry and brought it from being a shunned field into one that became recognized and incorporated into dental school curricula and training programs. Prior to the discovery of osseointegration, dental implant technology consisted of blade and transosteal implants.

— 1960: A biocompatible inert material, ceramic, was used in 1880, and it reemerged in 1960s in the newer forms. The brittle nature of this material caused it to fail. To overcome these problems, the monocrystalline forms were developed which were much stronger. These were basically developed in Japan and good results were claimed in the mandible. The implant soft tissue interface was similar to the between natural tooth and the gingival.

— 1962: Chercheve introduced another screw type of implant made of chrome cobalt, which became very popular. But it was unable to withstand any lateral forces.

— 1966: Linkow developed a blade type implant of chromium nickel and vanadium. These were single step procedures, where implants were introduced through the mucosa into the bone. Subsequently a lot of investigators tried to develop blades of vari-

ous designs and of different materials all of which resulted in varied success rates. Blade implants consisted of a metal blade that was placed within a bony incision that subsequently healed over the horizontally situated piece of metal but allowed a vertical segment to perforate the healed surface. Transosteal implants, the application of which was strictly limited to the mandible, consisted of a number of screws which were inserted into the inferior aspect of the mandible, some of which extended through and through into the oral cavity. Both of these implant types relied on mechanical retention, as it was heretofor unknown that metal could be fused into the bone

— 1967: Hodosh used acrylic resin in the form of a tooth and tested these implants on monkeys. Since acrylic was easy to shape and was resistant to corrosion unlike most metals, it was therefore the material of choice. These implants were made with a porous root type structure, which was said to allow ingrowths of bone, but unfortunately this was not the case.

— 1975: Blades, introduced in 1966–67, were made from titanium, ceramic (monocrystalline forms) and memory alloys, all being very biocompatible materials. In 1975: Hodosh and his co-workers developed implants made of a biocompatible material, vitreous carbon. These implants had a fibrous band, which was claimed to be well organized and which could compare favorably to natural periodontal ligaments, with added advantage of bone ingrowths since the material was biocompatible. These implants were used as a single tooth replacement inserting these into bone sockets. They were made from 99.99% pure carbon and this had a stainless steel sleeve for strength. Though there was a claim of 70% success in experiments on baboons, the results in clinical trials were not as successful.

— 1978: The first Dental implant Consensus Conference was held, sponsored jointly by the National Institutes of Health and Harvard University. It was a landmark event, at which retrospective data on dental implants were collected and analyzed; and criteria and standards for implant dentistry were established.

— 1982 in Toronto: Brånemark presented work that had begun 15 years earlier in Gothenburg. His discovery and application of osseointegration, or the biological fusion of bone to a foreign material, was unparalleled and such scientific documentation of implantology had never before been gathered. The Toronto conference brought widespread recognition to the Brånemark implant methods and materials and is one of the most significant scientific breakthroughs in dentistry since the late 1970s. The Brånemark System of dental implants was bought out and is currently available from Nobel Biocare.

— 1989: The Brånemark Osseointegration Center (BOC) was founded in Gothenburg, Sweden. Brånemark has also been honored with the Harvard School of Dental Medicine Medal for his work on dental implants in the United States and holds more than 30 honorary positions throughout Europe and North America, including the Honorary Fellowship of the Royal Society of Medicine in the United Kingdom. **Per-Ingvar Brånemark** was on born May 3, 1929. He is a Swedish orthopedic surgeon and research professor, touted as the "**father of modern dental implantology**." In 2003, he received an honorary doctorate from the European University of Madrid. He was the winner of the European Inventor Award 2011 in the category Lifetime achievement.

— Research of Dr. Branemark on the workability of titanium for orthopedic use led to development of dental implants of titanium. Titanium implants were placed into jawbones of dogs and fixed medical devices were fixed onto these. The results were evaluated at different time intervals (2). Brånemark's son, Rickard, has taken this success and is developing orthopedic prostheses in the form of artificial arms and legs anchored to the human skeleton.

Although the field of implantology was eschewed by dental academia until that time, the "extensive and w80 documentation of implant efficacy and safety" and "early replication by reliable, independent researchers" resulted in the widespread embrace of implantology by the dental community. Today: Implants are made predominantly of titanium (pure titanium or a Titanium alloy like: Ti-Al-V composition). Several procedures are available to increase surface area, i.e., to increase the contact surface to the bone and thus achieve better bone integration (osseo-integration). The prevailing implant forms are screws (also root-analogous) and cylinder implants. For a detailed historic prospective, the reader may consult: "Shulman, L.B., and T.D.Driskell, 1997. Dental Implants: A Historical Perspective. In: *Implants in Dentistry* edited by M. Block, J. Kent, and L. Guerra. Philadelphia – PA, USA: W.B. Saunders;" and "Brånemark, P.I. Introduction to osseointegration. In: *Tissue-Integrated Prostheses – Osseointegration in Clinical Dentistry*, edited by P.I. Brånemark, G. Zarb, and T. Albrektsson. Quintessence Publishing, Co. Inc., Chicago – IL – USA."

12.3 DENTAL AND PERIODONTAL DISORDERS AND DISEASES

Abfraction, abrasion (dental), abscesses of the periodontium, acid erosion, acute necrotizing ulcerative gingivitis, adenomatoid odontogenic tumor, aggressive periodontitis, ameloblastic fibroma, ameloblastoma, attrition (dental); **Bad breath** (halitosis), barodontalgia; **Calcifying odontogenic cyst**, cementoblastoma, cementoma, central odontogenic fibroma, cold sores, combined periodontic-endodontic lesions, cracked tooth syndrome;

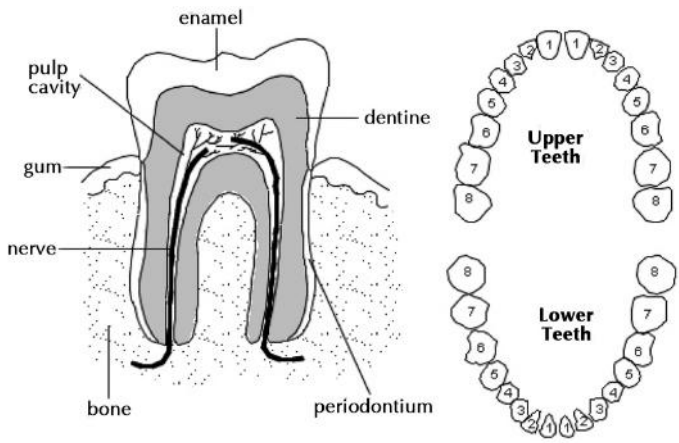


FIGURE 1 Anatomy of a normal tooth.

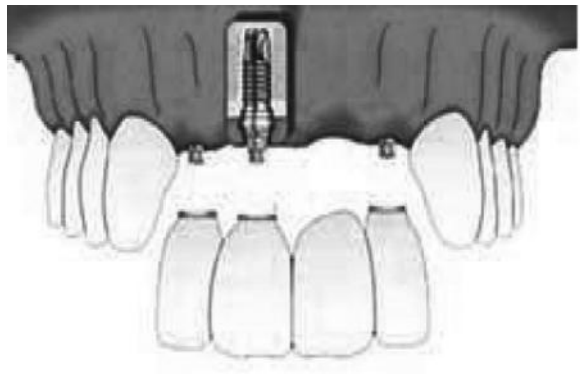


FIGURE 2 Front dental pieces attached via screws (12).

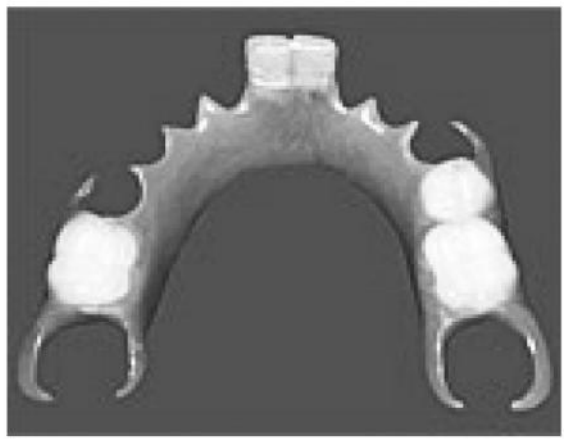


FIGURE 3 Dental prosthesis consisting of ceramic teeth (12).

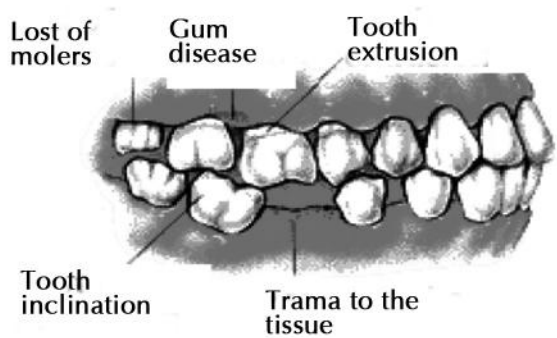


FIGURE 4 Causes of the loss of teeth (18).

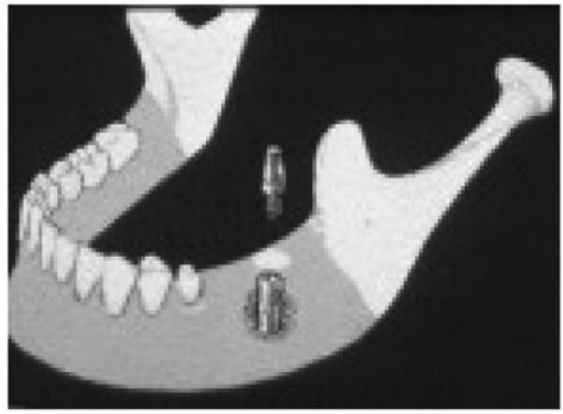


FIGURE 5 Mount installation (12)

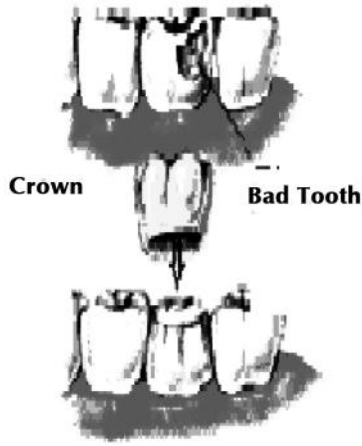


FIGURE 6 Crown installation (12).

Dental abscess, dental avulsión, dental barotrauma, dental caries, dental concussion, dental cyst, dental plaque, dental subluxation, dental trauma, dentigerous cyst, dentine hypersensitivity, dentition – permanent tooth loss, dentition- primery tooth loss, dentofacial anomalies, dermoodontodysplasia, desquamative gingivitis, drifting/loosening of teeth; **Early childhood caries**, epulis, erythrodontia, external resorption; **Fever blisters**, fracture of the tooth; **Gingival and periodontal pocket,** gingival enlargement, gingival recession, gingivitis, gingivitis – acute necrotizing (Vincent's gingivitis or trench mouth), gingivostomatitis, gingivostomatitis – herpetic, glandular odontogenic cyst, gum (Periodontal) disease, ganker sores; **Halitosis** or a foul taste in the mouth, hypercementosis; **Impacted wisdom teeth**, internal/external resorption of the tooth or adjacent teeth; **Keratocystic odontogenic** tumor; **Linear gingival** erythema; **Mouth olcers** and thrush; **Neonatal teeth**;

Occlusal trauma, odontodysplasia – regional, odontogenic cyst, odontogenic keratocyst, odontogenic myxoma, odontogenic tumor, odontoma, oral mucosa, oral torus, oral ulcer, Orson Hodge, overbite; **Palatal expander,** paradental cyst, peg-shaped teeth (Hutchinson's teeth), periapical abscess, periapical cyst, periapical periodontitis, pericoronitis, peri-implant mucositis, peri-implantitis, periodontal abscess, periodontitis, periodontitis – acute (early onset periodontitis), periodontitis – aggressive, periodontitis – cronic, periodontosis, peripheral odontogenic fibroma, Phoenix abscess, pink tooth of mummery, postextraction bleeding tooth socket trauma, pulpitis; **Riggs' disease**, root resorption, root sensitivity; **Segmental odontomaxillary dysplasia**, squamous odontogenic tumor, subluxation, swelling of the oral mucosa; **TMJ**, tooth abscess, tooth erosion, tooth eruption, tooth germ/cyst/tumor, tooth loss, tooth resorption, tooth sensitivity, toothache; and **Ulceration** of the oral mucosa.

12.4 PRESENT DENTAL TECHNOLOGY

12.4.1 TEETH MOVEMENT AND DAMAGE

The prosthesis (Fig. 3) is any artificial element that can replace a damaged or lost part of our body. Dentist advises the patient to take care of their teeth for good oral health. Yet, most of the persons do not follow the advice of the dentist. The part of work of a dentist is to fix or replace the loosen pieces. It is important to note that a dental prosthesis is part of a treatment that helps the recuperation of oral health. With the help of our teeth we are able to chew food. Dentures manipulate the function of our mouth and teeth. Also inside the mouth, there is a complex muscular system that gives movement to jawbone and the jawbone is able to rotate.

A dental prosthesis in a wrong position can damage the articulation. Also we cannot treat our teeth in our own way. For example, the more weight on the molar teeth will cause it to move abnormally. This abnormal movement will cause a pain. If we place prosthesis in the mouth with a diseased gum, after sometime the prosthesis has a good chance to fall off. Returning the mouth, after it has been damaged, to its original state using any method is called "curing the mouth" and the prosthesis or artificial teeth that are collocated in the mouth is part of the curing process.

12.4.2 OCCLUSION – PROSTHESIS

There are two types of treatments that are used in order to replace the lost teeth: Permanent prosthesis and provisional prosthesis (Figs. 3 to 5). A hold-all is a first piece that is placed on the teeth. It consists of molar teeth with a central hole that is placed over a previously sculpted to leave space for the prosthesis. The hold-all must fit the neck of the molar teeth to prevent future cavities. It also must fit with adjacent molar teeth. This process is called occlusion.

A **bridge or permanent prosthesis** consists of two hold-all joined together and one or more intermediate pieces that stay over the mouth gum touching it but not sticking to it. Using this method, we can replace lost molar teeth holding with the other molar teeth. Under the bridge, there is a space that is left open to facilitate the cleaning. Although this space cause a little pain, yet it is necessary for hygienic purpose.

If there are no dental pieces to grasp, the dentist will make a **provisional prosthesis** of plastic or metal. If some dental pieces are left, they would be held with hooks.

However, if it is a complete piece, it will adapt to all the texture that are in constant movement in the mouth. In full dental sets, a very good occlusion is necessary so that when the patient masticates, their teeth come up against other teeth making to loose.

12.4.3 CROWNS AND BRIDGES

Restoration treatments like crowns and bridges replace lost or damage teeth. When there is a lost tooth or a broken tooth, it is very important to replace it with an artificial tooth to restore the oral health.

Crowns (Fig. 6), also known as hold-all, are artificial covering (where they cover the visible portion of teeth). These are made of porcelain, metal, plastic or in combination of both. These are necessary, when the teeth are submitted to a conduct, treatment or it has any discoloration or it is broken.

Bridge (Fig. 7) is an artificial replacement of one or more natural teeth. To replace a lost tooth with a bridge, the teeth surrounding must be prepared using a crown (Fig. 6). The replacement and crown must be prepared first and put in the mouth as one piece. Once the bridge is glued, the patient cannot remove it. The work involves in making and installing a bridge and is similar to a crown. In some cases, a resin bridge called Maryland can be used. It is useful because it does not need any preparations of the adjacent teeth.

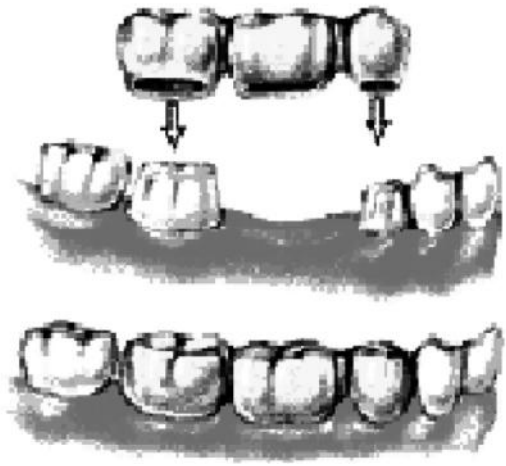


FIGURE 7 Bridge.

12.4.4 IMPLANTS

Implants can be described as “artificial dental roots.” In modern biomedicine, these are means of choice in treatment after tooth loss or for edentulous patients. An implant consists of three parts (1) as shown in Fig. 8:

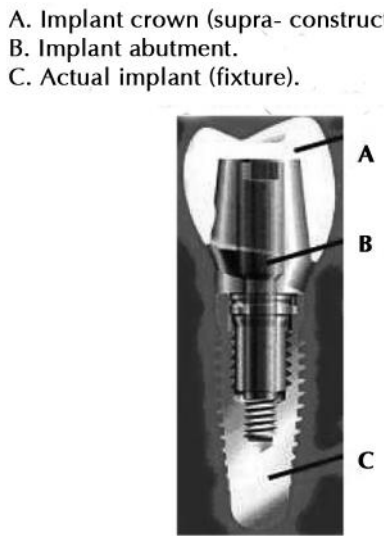


FIGURE 8 Schematics of an implant. (a) Implant crown (supra-construction). (b) Implant abutment. (c) Actual implant (fixture).

a. **The supra-construction:** Supra-constructions can be permanently attached to implants. Examples are: An individual crown or bridge, or partially removable; and over denture bar dental devices.
b. **The Implant abutment:** This part constitutes the actual connection between the implant fixture and the "supra-construction" (crown or bridge).
c. **The actual implants:** The implants in the actuality have some fixtures. It constitutes the supporting "pier" for tooth replacements. Implants are designed to imitate the natural tooth root and are anchored directly in the bone.

12.5 ORTHODONTICS

Orthodontics, formerly **orthodontia** (from Greek *orthos* "straight or proper or perfect;" and *odous* "tooth") is a branch of dentistry that is concerned with the study and treatment of malocclusions (improper bites), which may be a result of tooth irregularity, disproportionate jaw relationships, or both. Orthodontic treatment can focus on dental displacement only, or can deal with the control and modification of facial growth. In the latter case it is better defined as "dentofacial orthopedics." Orthodontic treatment can be carried out for purely esthetic reasons with regards to improving the general appearance of patients' teeth (Fig. 9). However, there are orthodontists who work on reconstructing the entire face rather than focusing exclusively on teeth. The use of digital models in orthodontics is rapidly increasing as the industry undergoes analog to digital conversions in record keeping. The University of Minnesota recently developed Three Dimensional Dental Models for Computer Automated Treatment Simulation that can be used to reduce the amount of human input needed for orthodontic treatment planning. This software tool has the ability to automatically segment

teeth from one another and the gums. Digital laboratories are currently being used by many orthodontists, but can be very expensive. This software provides an efficient and cost-effective method for completing the segmentation process.

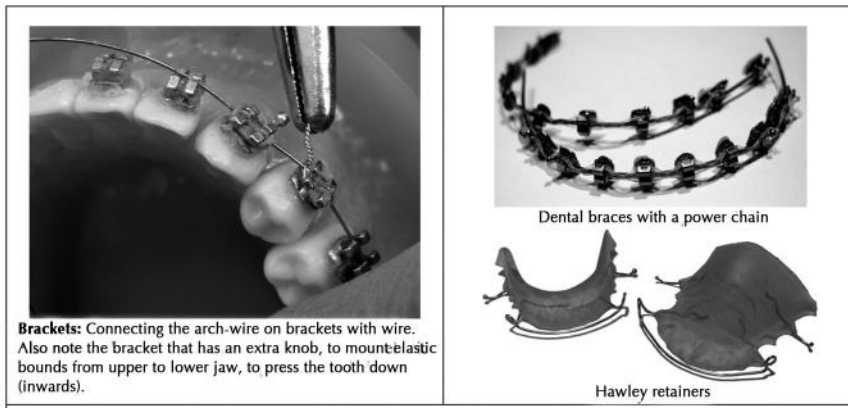


FIGURE 9 Orthodontics.

12.5.1 BIOMECHANICS OF TOOTH MOVEMENT

Mechanics is the science dealing with the action of forces on the form and motion of bodies. The forces are exerted by the orthodontic devices or by muscle contractions against the teeth or through intercuspation of the teeth. Any orthodontic appliance is a force system storing and delivering forces against the teeth, muscle or bone and creating a reaction within the periodontal ligament and alveolar bone that permits movements of the teeth. Any orthodontic appliance, when activated, delivers a force system. Any force system can, for analytical purposes, be reduced to one force, one couple or one force plus one couple (See any textbook on Engineering Mechanics: Statics). Thus, it is theoretically possible to analyze any orthodontic appliance force system.

12.5.2 BIOLOGICAL REACTION TO ORTHODONTIC FORCES

The biologic response to orthodontic forces in the adult is slower than in the child. The removal of occlusal forces is important in adult tooth movements and there is a need for light forces with longer periods of rest between adjustments.

1. Periodontal drift and physiologic tooth movement

During growth of the mandible and maxilla, the teeth undergo constant changes in position that require an adjustment mechanism so that a tooth can remain attached by the periodontal ligament to the alveolar bone in a continuous and uninterrupted manner. The movement of teeth includes eruption and vertical development as well as progressive drifting. The drifting movements of teeth contribute to the progressive and continue process of relocation of the dentition in relation to the growing, remodeling and relocating of facial bones. Just as teeth and alveolar bone drift together, the periodontal ligament itself undergoes a corresponding process of drift that permits differential movements between the root of the tooth and its surrounding alveolar wall

while maintaining continuous attachment between them. This complex process involves two basic and different mechanisms of drift; one is associated with resorbing alveolar surfaces and the other with depository surfaces.

Physiologic tooth movement is used to describe the movement of the tooth in the alveolar during function, the change in the tooth position during eruption and the transitional dentition and the natural changes in tooth position.

2. Factors in tooth movement

The **manner of force application***:* The magnitude, duration, and direction of force may be combined in various forms. For example we have the *continuous forces* that maintain approximately the same magnitude of force over an indefinite time; *dissipating forces* are continuous but demonstrate a decreasing magitude of force within a short period; and *intermittent forces* are associated with removable appliances and this forces is nonexistent when it is removed; and *functional forces* that appear against the tooth only during normal oral function.

The **magnitude of force application** varies with type of tooth movement. In this case the magnitude of the force determines the duration of the hyalinization. When excessively strong forces are applied, a longer initial hyalinization period will result as well as the formation of secondary hyalinized zone.

The **duration of force application** is an important factor, because the periodontal ligament must have recovery periods to replenish the blood supply to the ligament and to promote cell proliferation. A heavy force of short duration may be less damaging than a light, continuous force.

3. Types of tooth movement (31)

Tooth movements are classified according to the direction of force application. Often, orthodontic movements are countered by the intercupspation during occlusal function, resulting in jiggling and often hyper mobility. Teeth being moved may show no mobility until an occlusal interference is encountered. The mobility may be needed for occlusal stabilization in the final position.

a. The *tipping* movement during this, the crown and root are moved in opposite directions around a center of rotation within the root. Diagonally opposite areas of compression and tension are produced within the periodontal ligament. This is the best form carried out a light, continuous force.
b. Another direction is the *translation*. During the translation or bodily tooth movement crown and root are moved in the same direction at the same time. This movement usually is brought about by a couple.
c. *Rotation* is the movement of the tooth around its long axis. The rotation is very complicated tooth movement, difficult to effect and difficult to retain rotation presents the best effect by dissipating forces with periods of stabilization between activations of the appliance.
d. The *intrusion* is the movement of tooth into the alveolus. Very light forces are used in the intrusion of teeth and when done properly, little relapse is seen.
e. *Extrusion* is the movement of tooth out of the alveolus that is, the root follows the crown.

f. The *torque*, as used in orthodontics, is a movement of the root without movement of the crown. Torque may be produced by the use of rectangular wires in rectangular bracket slots or by adjuncts to a round wire. The effects of torque vary with the area of the root studied. Undermining resorption is more likely to be seen in the apical portion of the root, where the forces are the greatest. Since the force varies along the root surface, torque usually is expressed as the amount of force at the crest of the alveolar processes. Forces of 50–60 Gm, at the alveolar crest are satisfactory for most torquing movement.

4. Tissue response

In the initial reaction, it has been shown that some of the periodontal vessels are compressed a few minute after the application of orthodontic forces. The pressure of the tooth only rarely results in direct resorption of the bone at the pressure site. Compression of the periodontal ligament against the wall of the alveolus usually results in the area of the compressed periodontal ligament becoming cell free, and the movement of the tooth stops until the hyalinized tissue has been removed. The time necessary for undermining resorption of the bone and removal of the hyalinized tissue is roughly proportionate to the extent of the hyalinization.

Later on the secondary response the periodontal space is widened and direct resorption of bone typically is seen on the tension side a proliferation of osteoblasts presages the appearance of asteroid tissue, which is followed by new bundle bone.

The root resorption has three types: **Microresorption** is local, superficial confined to the cementum and routinely repaired; **Progressive resorption** involves increasing amounts of the apical end of the root; and **idiopathic resorption,** in which the root resorption is not related to the orthodontic forces.

5. Design of Appliances For Tooth Movements

Most orthodontics appliances derive their forces from bending of spring wire or from the torsional properties of wire. Elastics are another routine source of orthodontic forces. Screw forces are used much less frequently because these are difficult to control in the lower force range. Orthodontics forces may be applied to the tooth directly or by means of brackets or attachments (Fig. 9). When round wires are used in brackets, ordinarily there is control in two directions only. Rigid attachments, for example, with a rectangular wire and a rectangular slot, permit control of the tooth in all three directions.

When the orthodontic wire is shaped to make a simple spring and the forces in that spring are measured at different deflections, it is observed that the forces increase proportionately to the distance of the deflection, according to the Hooke's law: "the deflection is proportional to the load." Thus, in the orthodontic spring throughout the range of its normal action, the applied force divided by the deflection produces a constant known as the load deflection rate. Orthodontic springs, with a low load deflection rate, deliver more constant forces, since there is less change in force with each unit change in activation. This principle underlies the theory of the "light-wire" appliances. The ideal orthodontic spring has a large range of activation and a low load deflection rate. However, to design such an ideal spring into an orthodontic appliance, we need

to know several factors: The characteristics of the alloy from which the spring is made, the cross-sectional size of the wire, and the length of the wire.

In clinical practice, it is desirable to apply known forces over a predetermined distance and for a specified length of time. In order to achieve these goals, it is necessary to understand how the diameter of the wire and the length of the spring affect the characterictics of the spring (**F = δ*k**, where: δ = spring displacement and k = spring constant). The force created by deflection in a specific length of wire increase 16 times per deflection unit when the diameter of the wire is doubled. Increasing the length of the spring without altering the diameter has a dramatic effect on the load in the spring, since the force that is created is reduced to one-eighth when the spring length is doubled (31). Considerable variation in the force, duration of force expenditure, direction of force application and distribution of forces within the periodontal ligament is achieved by skillful use of loops and helices in the arch wires. Controlled tooth moments are achieved only when one has control of the moment-to-force ratio applied to the crown of the tooth it is this ratio that determines how the tooth is going to move, not the absolute force applied. Simple auxiliary spring applied to the naked crown of the tooth produce tipping, but it is uncontrolled tipping.

12.6 IMPLANTS ADVANCES

Stick Tech Ltd in 2003 introduced a new method of implant: The Direct Eversitck C&B Fiber Reinforced Bridge (Fig. 10).

12.6.1 REMOVABLE PARTIAL DENTAL DEVICES

Functional stability and the preservation of remaining alveolar bone are primary and often elusive goals when restoring the partially edentulous arch. The incorporation of dental implants for the partial support of removable prostheses (5) offers a practical adjunct in the fulfillment of these objectives as shown in Fig. 11. Treatment in which a removable partial denture is supported by natural remaining teeth in conjunction with osseo-integrated implants.

12.6.2 MARYLAND ADHESIVE BRIDGE

For many years, dentists had to reduce healthy teeth as abutments for fixed bridges. The Maryland Bridge is an ultra-conservative treatment option that enables the dentist to splint or replace missing teeth esthetically, with an absolute minimum of supragingival tooth modification. Combining a micro filled-composite resin cemented to acid etched enamel and an electolytically acid etched or silicoated cast metal framework, the Maryland Bridge improves the bond strength of the restoration three-fold over earlier perforated resin-bonded retainers. Current second-generation designs and tooth preparations, coupled with improvements in cementing resins, which rely on adhesive rather than an etched metal system, have provided even more exciting and reliable restoration possibilities, as shown in Fig. 12.

Adhesive cementation of alloy to the tooth structure allows the casting to be supported by abutment teeth. Bonding also prevents back displacement back along the path of insertion. Because displacement of the casting in all directions other than along the path of insertion is prevented by alloy engaging tooth structure, the framework

design limits the stresses placed on the looting agent and bond, dramatically increasing the longevity of the restoration (7).

12.6.3 FIXED BRIDGE OVER NATURAL BRIDGE

Natural line angles, embrasures, surface texture and occlusion all combine to make Natural Temps the most esthetic provisional available today (Figs. 13 and 14). The use of denture teeth ensures that the dentist has a full range of shade, mold and size options, allowing an exacting match with remaining dentition. Emergence profiles are carefully developed, aiding in tissue healing and improved oral health. Kind to soft tissues, the prosthesis can be adapted over time to new contours as gingival tissue heals and change (7).

12.6.4 TITANIUM OSSEO INTEGRATION AND PORCELAIN

This family of implants has undergone a tremendous development. They were tested and offered in different material compositions, since isolated studies have shown that materials other than titanium may integrate into living bone. Such materials included Aluminum Oxide, Vitallium, Commercially Pure (CP) Titanium, Titanium Alloys, even Sapphire. Today, the most accepted material for dental implants is high grade Titanium: either CP Titanium or an alloy. The titanium alloy implants tend to be stronger than the CP titanium implants, Figs. 15 and 16. The bone integration shows no difference to the two different types of titanium (8).

12.7 FOOD AND DRUG ADMINISTRATION REGULATIONS (14)

The device Quality System (QS) regulation covers the manufacture, storage (820.150), distribution (820.160) and installation (820.170) of finished devices.

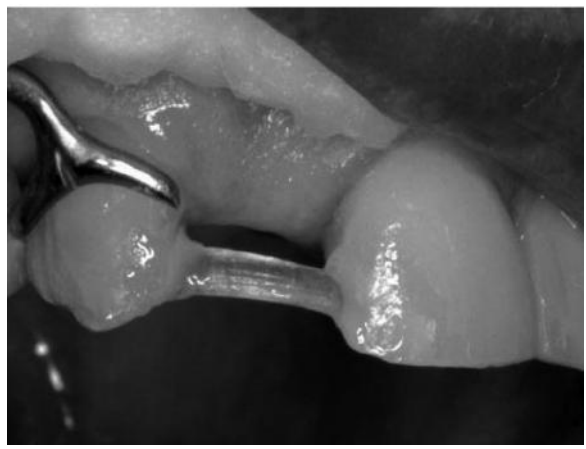


FIGURE 10 The glass fiber bundle (everStick®C&B) was tacked into the prepared teeth and light-cured for 5–10 sec. The whole fiber frame was covered first with flow composite, light-cured and then the layering of the pontic was done with a micro fill composite (4).

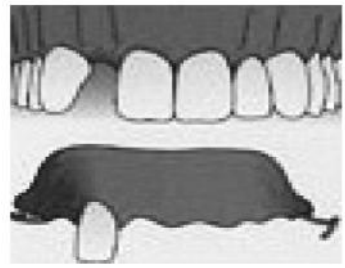


FIGURE 11 Removable partial prosthesis (6).

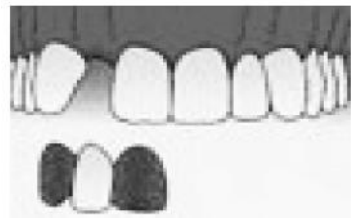


FIGURE 12 Maryland Adhesive bridge (6).

FIGURE 13 Fixed bridge over natural bridge (6).

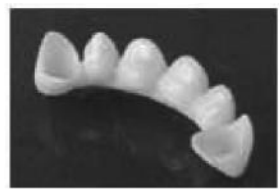


FIGURE 14 Fixed bridge over natural bridge (7)

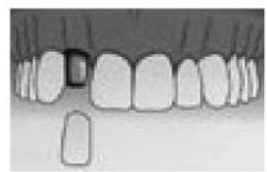


FIGURE 15 Titanium Osseo integration (6).

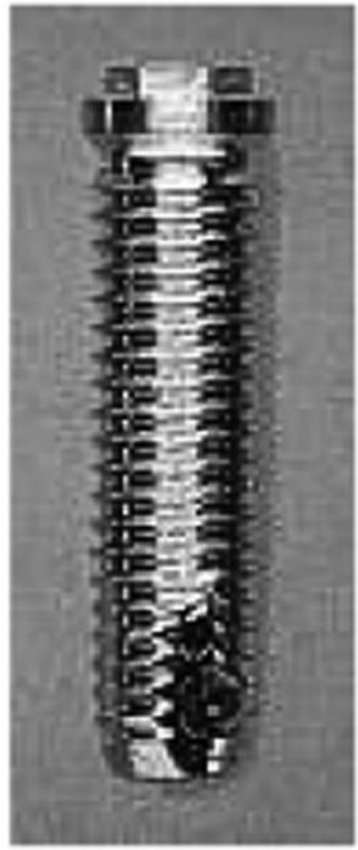


FIGURE 16 Pure solid titanium screw implants (9).

For manufacturers and importers, distribution is one of the most important steps in the quality system. After a product is distributed, a manufacturer rarely has direct control over the product or how it is used. Thus, it is important that controls should be in place to assure that only correctly labeled, packaged and approved finished devices are distributed and, if necessary, installed.

12.7.1 HOLDING AND DISTRIBUTION PROCEDURES

Section 820.160 requires that the purchase order should be reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Manufacturers should have a program to reduce problems. Marketing personnel should be adequately trained. Sales specification flyers and catalogs should be carefully written and kept current to reduce ordering problems. Incoming purchase orders should be checked and ambiguities and errors resolved. After receipt by appropriately trained personnel, orders should be reviewed immediately.

If purchase orders are reviewed late in the manufacturing process or just before distribution, the value of the review may be significantly reduced. When the customer includes specifications for particular orde, each specified parameter should be checked against the corresponding parameter for the device. A checklist of device parameters may be a helpful tool for this review and should be filed with, or keyed to, the purchase order.

The QS regulation (820.60), identification, requires manufacturers to set up and maintain identity control of their products from component receipt, production, distribution and through installation to prevent mix-ups. The regulation also requires that written procedures be provided for control and distribution of finished devices (820.160). The purpose of this requirement is to assure that only approved devices are distributed. Each manufacturer should determine what written procedures are needed to assure that only "approved for release" devices are distributed from the manufacturer. If a manufacturer believes written procedures will not contribute to assuring that only Approved for release devices are distributed by their manufacturer, they should be able to defend their decision. For example, the control is integrated into the activities required to package the device or to complete the device history record.

This flexibility is allowed by section 820.5, Quality system, of the QS regulation. Many manufacturers mark their released finished devices or identify them by location or packaging so that a simple visual check is sufficient to indicate whether the product is acceptable to release for distribution. For example, radiation-emitting electronic products are subject to a performance standard. The application of the certification label is often the last step in approving product release for distribution, and this label is used to distinguish such devices. After final release, the crating of large equipment is a very distinguishing feature. These types of operations may preclude the need for a separate written procedure.

For interstate contract sterilization, 21 C.F.R. section 801.150(e) requires a written agreement between the parties which details the necessary procedures to help prevent the erroneous release of packaged and labeled "sterile" but not yet sterilized devices that appear to be, but are not, ready for release. Regardless of whether 801.150(e) applies, the QS regulation requires controls, as necessary, to prevent mix-ups in complex situations such as contract sterilization. For consistency, a contract as described by 801.150(e) is commonly used by manufacturers for interstate and intrastate shipments. Compliance with such a contract satisfies the applicable GMP requirements.

Sometimes manufacturers need to ship "finished devices" that have not been officially released because the final test data is not yet available. The critical factor is that the device still remains under the control of the manufacturer. The most common example occurs when a manufacturer is waiting for the results from biological indicator tests. FDA permits manufacturers to ship such devices under quarantine to their own controlled warehouses where the devices may be readily recalled prior to any use, if the need arises. Manufacturers should not ship nonreleased devices to routine distributors or anyone outside of their direct control. Non-released products or products on "hold" for any quality reason should be controlled to prevent release. A suitable control is quarantine with a label on the units to indicate their status.

12.7.2 WAREHOUSE STORAGE

Storage should always be done under systematic, orderly conditions (820.150). Manufacturers should use a first-in, first-out (FIFO) distribution system when fitness for use of a device deteriorates over time (820.150).

When a controlled environment is necessary to prevent abnormal deterioration, the environment should be specified, controlled, and monitored according to sections 820.70(*c*). Environmental specifications, such as storage temperature, should be included in the device master record.

The storage and handling of devices to be distributed may involve extensive activities (820.140 and 820.150). For example, damaged, recalled or returned devices should be suitably marked and segregated from devices acceptable for release (820.86). Returned devices should be handled and stored such that the cause of failure or other useful information is not destroyed. Returned defective devices should be formally investigated according to 820.100 Corrective and Preventive Action and any associated complaints investigated according to 820.198. Therefore, manufacturers will need controls to assure that returned defective devices do not dead-end in the warehouse, but are expeditiously routed to the appropriate department for evaluation, investigation, conclusions and follow-up

12.7.3 DISTRIBUTION RECORDS

Quality System section 820.134, Device History Record (DHR), requires manufacturers of devices to maintain basic records for:

Dates of manufacture.

- The quantity manufactured.
- Quantity released for distribution.
- Acceptance records.
- Primary identification labels and labeling used.
- Any device identification and control number used.

Section 820.160, Distribution, requires the following records:

- Name and address of the initial consignee.
- Identification and quantity of devices shipped.
- Date shipped.
- Any control number used.

Some of the above information necessary for the distribution records is a duplicate of Device History Record (DHR) requirements. These duplications may be copied or transferred electronically from the DHR. If appropriate, a manufacturer may combine the records by adding the distribution information to the DHR. In addition to the above requirements, manufacturers of implantable devices and life sustaining devices, the failure of which during use could result in significant injury to the user, are required to establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and, where appropriate, components (820.65). Distribution records may be the same as, or part of, the normal business records. Generation of a separate record is not required unless the business records are not readily available, e.g., not maintained at the same establishment as the device history record and not

readily retrievable electronically. Many manufacturers also keep distribution records for billing and market survey purposes.

Manufacturers of radiological electronic products listed in 21 CFR 1002.1, Record and Reporting Requirements By Product, shall maintain distribution records that will enable them to trace specific products or production lots to distributors, or to dealers in those instances in which the manufacturer distributes directly to dealers. Distribution records shall be kept for a period of time equivalent to the design life and expected life of the device, but in no case less than two years from the date of release for commercial distribution by the manufacturer (820.180(b)). The intent of this requirement is support for potential repairs, corrective actions and recalls. Each manufacturer should make a prudent decision whether to discard records or keep all, or part, of them for a longer period. When requested, distribution records shall be made available to FDA investigators for review and copying during normal business hours.

12.7.4 DEVICE INSTALLATION

Section 820.170 on installation requires that each manufacturer establish and maintain adequate installation and inspection instructions and, where appropriate, testing procedures. The purpose of this requirement is to ensure that the device is properly installed and will perform as intended after installation. This regulation applies to medical device systems and complex devices that require set up and adjustment at the location where they are to be used. For example, before a diagnostic X-ray machine can be used, it has to be installed and adjusted and the performance checked. Cardiopulmonary bypass machines also require set up and adjustment at the user location.

Manufacturers of such devices shall:

- Install the device, or have it installed by a representative.
- Inspect and test, as appropriate, the device after installation to assure the device will perform as intended.
- Provide adequate instructions and procedures for proper installation by another party.

These instructions and procedures for proper installation by the manufacturer's representative, user, or third party (820.170) shall include instructions on how to determine that the installed device is safe, performing satisfactorily and ready for use. Safety checks at installation refer to safety aspects directly related to the installation and setup activities and not to intrinsic safety features that have already been checked during final acceptance testing at the factory.

The instructions and procedures shall be distributed with the device or otherwise made available to the person installing the device. Such procedures and instructions are part of the device master record and generally include a checklist for the installer to make certain that all necessary installation and checkout activities have been performed correctly. The installer should complete the checklist. If available to the manufacturer, the filled-in checklist or other installation records are part of the device history record.

12.7.5 EXHIBITS

Various forms to show that devices are finished and may be released or stopped from release and a list of some traceable devices are briefly described below and then exhibited.

12.7.6 FINISHED PRODUCT RELEASE FORM

This exhibit shows an example of a finished product release form, which is actually a checklist for the manufacturing and QC departments of an in vitro diagnostic manufacturer to show that all required processes have been completed. The checklist acts as a reminder of the acceptance forms that are needed for a product and has space for the manufacturing and QC people to indicate that these forms have been completed and reviewed. Finally there is space for the designees to approve or disapprove the lot for release and for comments, if needed.

12.7.7 RELEASE TO FINISHED GOODS/SHIPPING

This exhibit is a release form as described above except that it is for various hardware products. The employee writes in the specification for the product being released.

12.7.8 PRODUCT SHIPPING HOLD

This exhibit is an example of a form used to stop the shipping of a finished device for reasons related to safety, performance, reliability, regulatory compliance, or other quality requirements.

12.7.9 RELEASE FROM PRODUCT SHIPPING HOLD

This is a form used to release a finished device from a stop shipment order. Because stop orders are always significant, this release form requires a signature by key management.

12.7.10 PARTIAL LIST OF TRACEABLE DEVICES

This exhibit lists many of the devices for which a manufacturer must adopt a method of device tracking and the citation to 21 C.F.R. for the device.

It is required that implantable devices and life sustaining devices, whose failure during use as described on the label, could result in significant injury to the user, establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices. Where appropriate, this traceability rule also applies to components. These procedures should facilitate corrective action. This identification should be documented in the device history record. Many of these devices were formerly called critical devices.

12.8 BIOMATERIALS IN ORTHODANCY

Orthodoncy makes use of three main materials: Stainless steel, ceramic (also know as the clear braces), and gold. Chemical composition of some dental material is as follows:

X12CrNi177	Ceramic alloy	Al_2O_3	Alumina
Ti6A14 V	Titanium alloy	ZrO_2	Zirconia
HGC-3	Amalgam		

The Alumina and Zirconia are used cosmetically, while the SSs are the traditional materials for braces (Fig. 17). Ceramic braces are made of a high tech glass-like

material developed as a spin off material by the NASA space program. A clear or tooth colored tie is used with ceramic braces in order to maintain the camouflage theme of the braces. Ceramic braces are guaranteed not to stain by the manufacturer. However, some foods, liquids (coffee, coke) or smoking may stain the cement that holds the braces to teeth. Gold braces are similar to stainless steel braces with the exception of being gold-plated. Many patients want to make the ultimate fashion statement. There are also gold wires available for this type of orthodontic appliance. Another material used in orthodoncy is cements. Cements are used in many forms in the applications of dental devices. Cements are the sole adhesive that sticks the base of the braces onto the patient's teeth in order to keep the braces in position during the extensive treatment. Cements may be stained by wrong usage. As a key factor within dental applications, much time is invested in developing strong, stainless and long lasting cements.

Orthodoncy is not the only application of dental devices. Odontology also plays a key role within the field of dental devices. Odontology has found its place well within modern history. Dentures, dental crown, bridges, and root canals, among others, are part of odontology. Many people use dentures or teeth cover. George Washington was famous for not smiling while his picture was being painted. This was due to the fact that he wore dentures. Back in his times dentures were made out of wooden boxes. Thankfully, times have changed and in modern societies dentures are not to be ashamed of. In some cases, people, have been known to pull out their good teeth in order to have them replaced by a perfect pare of dentures (15).

In some cases, people have tried to show their reaches by investing thousands of dollars in their teeth. They do this by making golden teeth covers. Some even go to the extent of making the teeth covers out of platinum encrusted with diamonds.

Similar to braces, dental devices are made out of an assortment of materials. Such materials include metals, but the prime materials used in dental devices are made of ceramics. There is more than just one form of ceramics that are used in dental devices. Dentures, crowns, and bridges all have their own unique ceramics (6).

Dental devices are used for an array of purposes: Improving a person's health and personal hygiene; and cosmetic reasons. Both purposes are justifiable and furthermore bring about different usages and different materials in order to produce a desired dental device (15). Choosing a material for dental devices is not as easy as it would be for a traditional material scientist. Most material scientists are concerned with materials that fit the established requirements, but for them to be cost effective as well. Yet, a material scientist that deals with dental devices must take into consideration the biocompatibility of materials. Because of this, these scientists must use materials that do not react negatively with the human body, but at the same time are functional.

12.8.1 STAINLESS STEELS

Stainless Steels have many usages, but their most useful characteristic include such properties of high strength and the control of surface hardness and other physical properties which may be possible through suitable heat treatments. In other words, steel may withstand harsh environments that induce elevated temperatures (Fig. 18). A limitation of steel is the tendency to corrode also known as rust. Steel is an alloy of iron (Fe) and carbon (C). Iron is the major component and the carbon content is less

that 1.6% (by weight). Other alloying elements may be present. If the principal components are Fe and C it is termed a plain carbon steel. The steel alloy contains other important alloying elements. Alloy steels are formulated for special properties like the corrosion resistance. Materials in which the C content exceeds 1.6% are termed cast irons (Table 1).

12.8.2 CERAMICS

For dental devices, three types of ceramics are used, but are not exclusive to: Dental porcelains, glass-ceramics, and ceramics and glass. Dental porcelains are presented as glass powders featuring particle sizes ranging 1–80 microns (approximately). When porcelains are mixed with glasses, the system is noncrystalline and acts as a supercooled liquid of high viscosity at room temperature. The structural basis of dental porcelain can be described as glass-like silica (SiO_2), which has been chemically modified to yield suitable physical and chemical properties.

Dental porcelain is a brittle material. All brittle material shares the same characteristic, with low tensile strength. Their tensile strength is reduced from its theoretical value by the presence of cracks and pores. These defects may be on the surface, or within the body of the material. Maximum strain before failure is of the order of 0.1%. The strength of dental porcelain is usually determined by a flexural method or transverse strength. Internal weaknesses may be reduced by mixing in partial vacuum vacuum-fired porcelain, with improved esthetics and strength (Fig. 19).

Glass-ceramics are materials based on the observation that suitably formulated glass bodies can be transformed into a polycrystalline system by a heat treatment. The resulting material is tougher, both in terms of mechanical and thermal insult, than the parent glass object. The naturalness of the process is due to the lower energy of the resulting semicrystalline system. Mechanistically, the transformation requires the presence of a nucleating agent in the glass, and the heat treatment is called ceramming. The glass-ceramic is at least 50% crystalline. The surface of the translucent cerammed crown generally requires to be characterized with porcelain.

12.8.3 TITANIUM ALLOYS

Titanium is immune to corrosion due to environment. It also exhibits exceptional resistance to a broad range of acids, alkalis, natural waters, and industrial chemical. The combination of high strength and low density results in exceptionally favorable strength-to-weight ratios for titanium-based alloys.

The specific weight of titanium is about two thirds that of steel and about 60 percent higher than that of aluminum. In tensile and sheet stiffness, titanium falls between steel and aluminum. But titanium's strength (80,000 PSI for pure titanium and 150,000 PSI and above for its alloys) is far greater than that of many alloy steels, giving it the highest strength-to-weight ratio of any of today's structural metals.

Titanium and its alloys have proven to be technically superior in a wide variety of industrial and commercial applications in such fields as aerospace, architecture, sporting equipment, military hardware, watch making, eyewear, medical implants, dental products and more (Table 2).

The physiological inertness of titanium makes it available as a replacement for bones and cartilage in a variety of surgeries. Titanium is used for heart valves, pace makers, dental implants, artificial hips and joints. Titanium is also used in surgery equipment and wheelchairs. Titanium is used in metallic alloys as a substitute for aluminum because of its strength and lightweight, along with its heat and corrosion resistance.

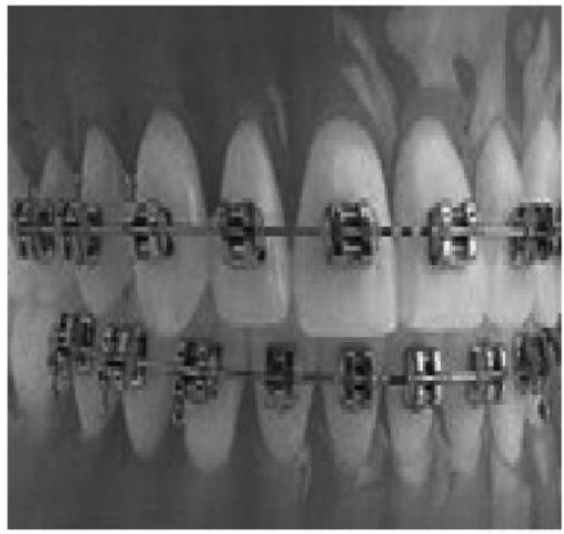


FIGURE 17 Sample of braces (22).

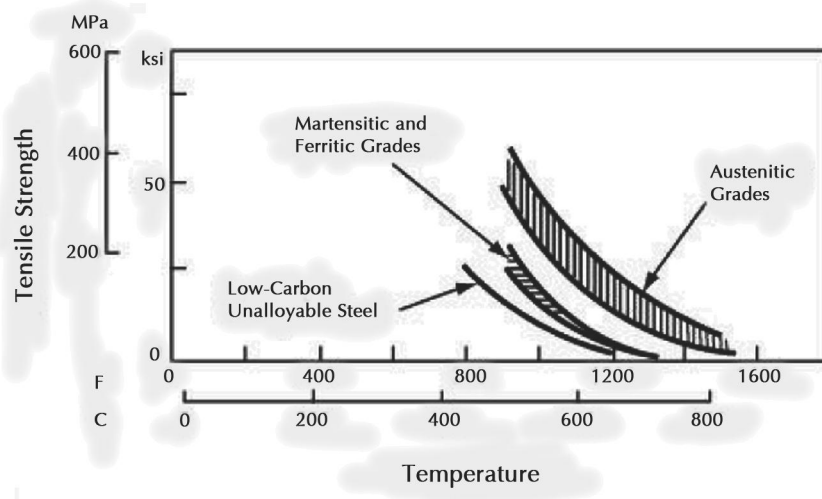


FIGURE 18 Tensile strength vs. temerpature of SSs (27).

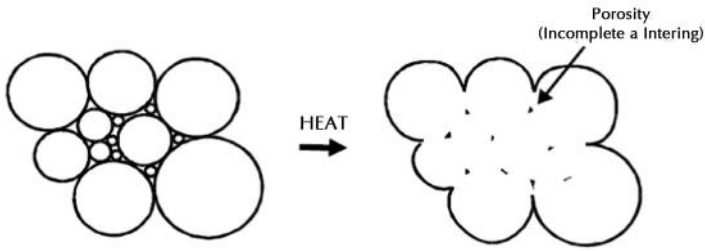


FIGURE 19 Representation of how to strengthen porcelains (25).

TABLE 1 Properties of stainless steel alloys (2).

Alloy	Condition	Tensile Strength (MPa)	Yield Strength (MPa)	Elongation (%)
X10Cr13	Hot Finish	275	485	20
	+ annealed			
	Cold Finish	275	485	16
	+ annealed			
X20Cr13	Hardened	1480	1720	8
	+ tempered 204°C			
X20CrNi172	Hardened	1070	1370	16
	+ tempered 260°C			

TABLE 2 Properties of Titanium alloys (2).

Alloy	Condition	Tensile Strength (MPa)	Yield Strength (MPa)	Elongation (%)
Ti5 Mo5Zr3Al	SHT at 840°C	870	882	20
	SHT at 740°C	968	975	16.9
Ti30Ta	Annealed at 1100°C	650	800	8
	Annealed at 1200°C	660	800	8

SHT = solution heat treatment

12.8.4 FINITE ELEMENT MODEL (FEM)

In order to improve the clinical performance of the implant systems it is important to identify the factors that could lead to their failure. Implant failure can be due to biological or mechanical reasons. Biological complications (i.e., bacterial infection, improper surgical placement) may damage osseo-integration, while the mechanical ones involve the loosening or the fracture of one or more components of the implant system.

The accuracy of the structural integrity of implant systems plays an important role in their planning stage, being useful to establish if a device can withstand the functional stress. This can be checked either by mechanical tests or by a computational structure analysis. The most common method is a FEM (8) to reproduce a standard experimental set-up for the evaluation of the mechanical failure of a dental implant system. A typical example is shown in Fig. 21. The characteristics of the simulated models are: precise reproduction of the implant system, use of elastoplastic model for the material description, correct definition of the contacts and the existing tolerance among the different system components, reproduction of the preloading stress condition.

12.8.5 MECHANICAL PROPERTIES (2)

Metallic biomaterials possess the outstanding property of being able to endure tensile stresses, which in the case of alloys, may be extremely high and also of dynamic nature. The main requirements that must be fulfilled by all biomaterials are: Corrosion resistance, bio-compatibility (bone in growth), bio-functionality (adequate mechanical properties, especially fatigue strength and a Young's modulus as close to that of the bone as possible), process ability and availability. These requirements are fulfilled by the various customary groups of biomaterials. Universal tensile testing machine for analyzing mechanical integrity of dental devices materials is shown in Fig. 21. A typical stress – strain curve is indicated in Fig. 22.

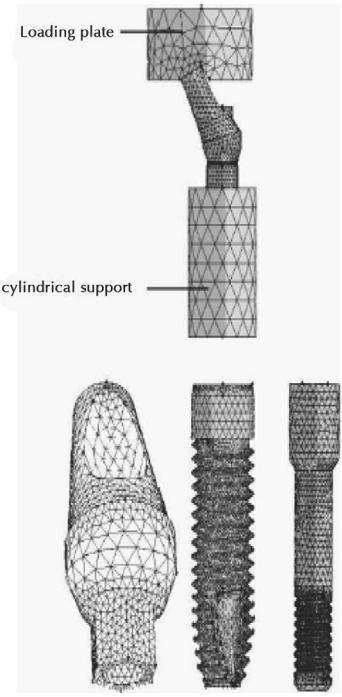


FIGURE 20 Three dimensional models of dental devices (8).

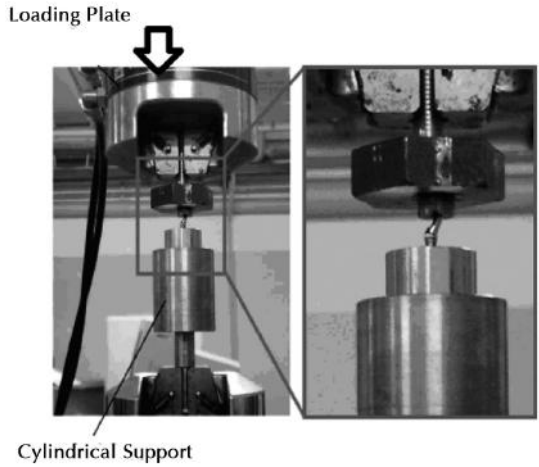


FIGURE 21 Universal tensile testing machine for analyzing mechanical integrity of dental devices materials (23).

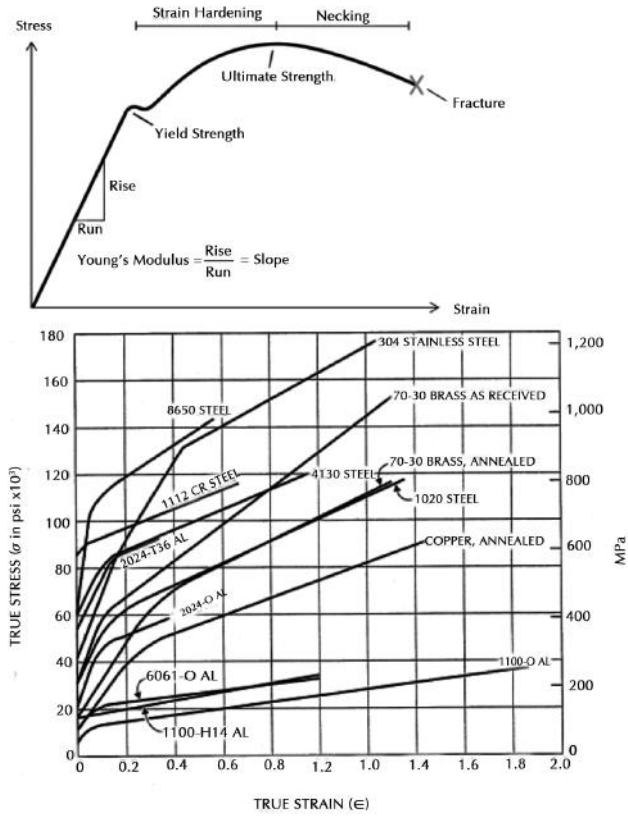


FIGURE 22 Stress vs. strain relationships for stainless steels (9).

In comparison the different materials show a different behavior according to the demands. A corrosion resistant material may not necessarily be biocompatible and contrarily, a more biocompatible material may be less corrosion resistant. Especially fretting corrosion may pose a problem in articulating devices like orthodoncy.

Often unique characteristic properties of a material are responsible for its application. Typical examples are the amalgams, which inspite of the reduced corrosion resistance and biocompatibility, used over a long period of time for dental restoration. Amalgams exhibit good process ability provided by the ability to amalgamate with mercury at room temperature within a short period of time (2).

12.8.5.1 CERAMICS MATERIALS (2)

Oxide ceramics exhibit superior mechanical properties, corrosion, and wear resistance. Since the oxides are the highest oxidation state of the metals, they are stable in the most invasive industrial and biomedical environments. Alumina and zirconia are used as load-bearing hard tissue replacements and fixation implants in dentistry and surgery. The Oxide ceramics are used in the following biomedical applications:

1. Alumina:
2. Hip ball and cup
   - Knee joint
   - Bone screws
   - Dental implants
   - Dental crowns and brackets
3. Zirconia
4. Hip ball
   - Dental implants
   - Dental post, brackets and inlay

Although alumina is chemically more stable, yet it is mechanically weaker than zirconia. The chemical stability of alumina is related to its phase stability, whereas the phase changes of zirconia results in strength and wear resistance. Release of substances from zirconia and alumina implants to the surrounding tissue is very low and neither local nor systemic effects have been reported. Resulting from a strong chemical bond between the Al and O ions, as expected from the value of heat of formation (–400K cal/mol), Al_2O_3 has a high melting point, the high hardness among known oxides, and high mechanical strength, (Tables 3 and 4).

Zirconia ceramics have a high density because of the heavy zirconium ions, and a low micro hardness and elastic modulus, together with high strength and fracture toughness compared to other ceramics including alumina. The superior mechanical strength provides the possibilities for producing ceramics devices of sizes below 32 mm.

Increase of both strength and fracture toughness can be obtained by using the tetragonal-monoclinic phase transformation of metastable tetragonal grains induced by the presence of the stress field ahead of a crack. The volume change and the shear strain developed in the martensitic reaction were recognized as opposing the opening of the crack and therefore acting to increase the resistance to crack propagation.

Alumina and zirconia ceramics have been used for root analog, endosteal screws, blades and pin-type implants. The root and blade from dental implants used during the 1970s tended to fracture after a few years in function. Although initial testing of these

polycrystalline materials showed adequate mechanical strength, the long-term clinical results demonstrated functional limitations related to material properties and implants design. However, single crystalline alumina showed mechanical strength superior to that of polycrystalline alumina. It allows a much higher load. One-stage dental implants of single crystalline alumina are used with a high success rate. Dental implants of zirconia have not been widely used clinically although zirconia has a similar strength and a much higher fracture toughness in addition to lower cost of production compared to single crystalline alumina. The term dental implant is used only for the material in contact with bone and soft tissue. Alumina and zirconia are also used in other dental application, alumina ceramic crown, zirconia dental post, and recently a dental inlay of zirconia was introduced. Orthodontic brackets made of oxide ceramics were also produced, tested and used clinically. Unfortunately, tooth surface damage was observed when the brackets were taken away. Because of this, modification of the debonding technique is under development.

12.8.5.2 DENTAL RESTORATION MATERIALS

By definition amalgam is an alloy of mercury with one or more other metals. Dental amalgams are produced by mixing an alloy powder with mercury. This alloy powder is called *amalgam* and the composition of amalgam denotes the composition of the powder. Amalgams for dental restoration are classified by the copper content in two basic types:

- Low-copper type, < 6 wt% Cu: Used since the late nineteenth century.
- High-copper type (nongamma-2 amalgam), > 6 wt% Cu: Used since 1960.

The result of the amalgamization is a microstructure constituting of un-reacted Ag_3Sn and Ag-Cu surrounded by a layer of Cu_6Sn_5 and the γ_1 matrix. The microstructure of the one-component nongamma-2 amalgams is similar to that of the mixed alloy except that the Cu_6Sn_5 particles are decomposed in the γ_1 phase and form no layer.

12.8.5.3 NICKLE – CHROMIUM ALLOYS

The Nickel – Chromium (NiCr) alloys in dentistry are generally used for porcelain veneered and un-veneered crowns, fixed and removable partial dentures and bridgework. The requirements for this specific application determine the chemical composition. The corrosion resistance of the NiCr-alloys is provided by the chromium content, which produces a passive oxide layer on the surface. Beryllium is added as a solid solution strengthener and supports the self-fluxing at the porcelain veneering temperatures. Aluminum also produces a passive oxide layer, aids in the bonding to the porcelain and strengthens the alloy due to the precipitation of Al-Ni_3.

The wide composition range results in an equally wide range of physical and mechanical properties (Table 3). The high rigidity and strength of these alloys are compared to that of the precious metal alloys make them suitable for the production of dental devices.

12.8.5.4 STAINLESS STEELS (9)

Stainless steels are characterized primarily by the corrosion resistance, high strength and ductility, and high chromium content.

This characteristic is especially useful for dental devices because the metal is in constant contact with an environment that causes rust. Yet the higher content in stainless steels reduce the corrosion resistance, because of this most dental devices uses stainless steels with low carbon content (Fig. 22 and Table 3).

12.8.5.5 TITANIUM ALLOYS (7)

Titanium and titanium alloys are noted primarily for outstanding strength-to-weight ratios, elevated temperature properties and, corrosion resistance. They also possess high rigidity-to-weight ratios, good fatigue strength and toughness and, in some cases, excellent cryogenic properties. Because of these characteristics and improved fabrication technology, titanium and its alloys are now important materials for dental devices (Table 3).

As shown, yield strength ranges from 186–586 MPa (27,000 to 85,000 psi) for commercially pure titanium alloys, in dental devices (Fig. 23). Titanium and its alloys are at least as strong in compression as they are in tension. For commercially pure titanium, compressive yield strength is about equal to tensile yield strength, while other alloys may exhibits slightly higher compression strength. Shear strength of titanium alloys is normally 60–70% of ultimate tensile strength. The bearing yield strength of titanium alloy sheet is roughly 1.2 to 1.6 times greater than the tensile strength for and E/D value of 1.5. As the E/D values change so does the value of the bearing strength. Under normal atmospheric conditions, the endurance limit of wrought, annealed titanium alloys is 0.5 to 0.65 times the ultimate tensile strength.

TABLE 3 Properties of biomaterials (2).

Properties	Units	X12CrNi 177	Ti6A14 V	Amalgam	Ceramics	
					Al_2O_3	ZrO_2
Thermal expansion coefficient	$10–^6/C$	17	8.6	25	6.5	10.1
Thermal conductivity	W/m-K	16.2	6.5	23	38.7	3.1
Specific heat capacity	J/g-°C	500	560	0.28	N/A	0.122
Shear modulus	GPa	N/A	N/A	188	N/A	27.4
Young's modulus	GPa	193	100–110	100–105	366	201
Density	g/cm^3	8.0	4.43	18.4–19.5	3.98	6.08
Poisson's ratio	—	0.27	0.33	0.35	0.26	0.30
Hardness	GPa	492	310	161	22	12.2
Tensile yeild strength	MPa	205	870	N/A	119	15.5
Ultimate tensile strength	MPa	515	950	54.7	310	420
Ratio: Yeild/tensile strength	—	0.40	0.92	N/A	N/A	N/A
Elongation of fracture	%	40	28	N/A	N/A	N/A
Reduction of area	%	N/A	25	N/A	N/A	N/A

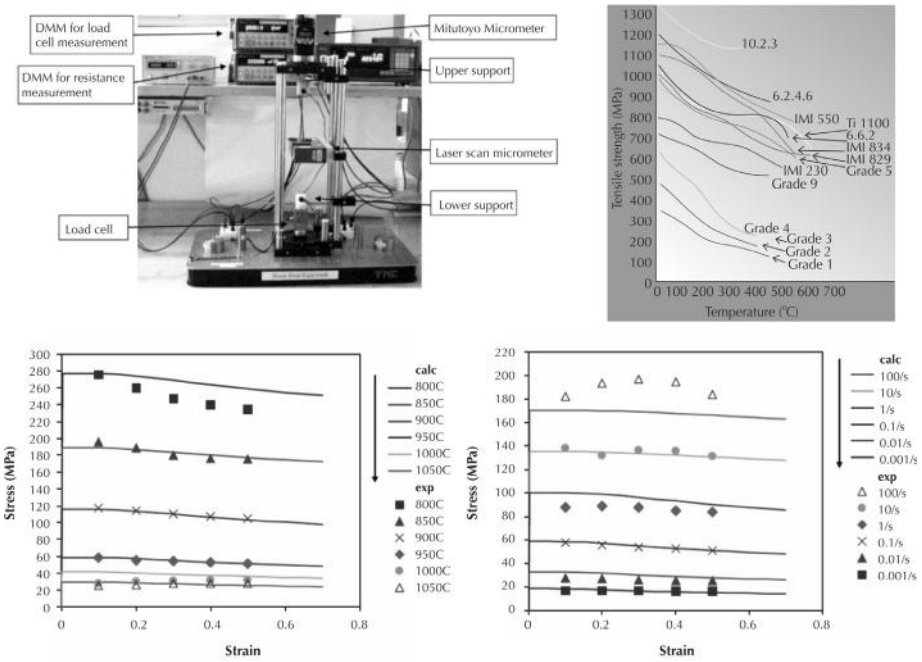


FIGURE 23 Strain versus stress (MPa) for Titanium alloy.

The hardness of commercially pure wrought titanium is usually less than 120 Brinell-hardness (Bhn) for pure grade. The hardness of other commercially pure grades range from 200 to 295 for wrought material and 200 to 220 for casting material. The tensile modulus of elasticity for commercially pure titanium is in the range of 15,000 ksi. The ranges of the rigidity of titanium alloys differ from alloy to alloy due to there manufacturing (Fig. 23). The impact resistance and fracture toughness of titanium alloys are inversely affected by increasing strength levels and interstitial content. Charpy V-notch impact strength is in the range of 11 to 40 ft-lb (14.9 to 54.2 J). A number of titanium alloys show a high degree of fracture toughness or resistance to crack propagation.

The thermal conductivity of titanium alloys is roughly half that of the unalloyed metal and increases with increasing temperatures. Thermal conductivity of pure titanium is 15.6 to 17.3 W/mK, which is uniquely similar to austenitic stainless steels, and unlike titanium alloys is relatively unaffected by increasing temperatures.

The thermal expansivity of titanium and its alloys is relatively low, ranging from 8.6×10^{-6} to 9.54×10^{-6} m/m/K within a temperature range of 58 to 393°K.

12.9 CONCLUSIONS

Orthodancy is a multimillion-dollar industry that involves high technology and new innovation. New materials that are stronger, more durables, and biocompatible are being evaluated in order to keep up with the high demands of dental industry. More and

more patients are being introduced to orthodoncy. It is therefore extremely important to develop new techniques and materials that do not scarify the quality of the procedure. Biocompatible materials are essential for dental devices. Some materials have specific usages within the human body. For example, there are materials that are ideal for usages in dental devices, but these same materials may not be as effective in other biomechanics applications such as stents. The greater parts of dental applications are made from stainless steels and titanium alloys.

12.10 SUMMARY

Dental prostheses are used when the patient has damaged or lost one or several of their teeth. The prosthesis replaces the original tooth and has the same function as the original tooth. Dental prosthesis is made of materials such as: stainless steel, titanium, ceramics and other types of metal alloys. These materials are selected on the basis of strength, resistance, biocompatibility, modulus of elasticity and tensile strength.

KEYWORDS

- **Amalgamate**
- **Athermal**
- **Austenite**
- **Bone formation**
- **Braces**
- **Bridge**
- **Brinell hardness**
- **Cartilage**
- **Casting**
- **Ceramic**
- **Coefficient of thermal expansion**
- **Copper alloy**
- **Crown**
- **Cryogenic**
- **Density**
- **Dental anatomy**
- **Dental device**
- **Dentistry**
- **E/D ratio**
- **Electrical conductivity**
- **Endosteal**
- **Face center cubic**

- **Fatigue**
- **Fatigue limit**
- **FCC**
- **Fibrous tissue**
- **Forging**
- **Hardness**
- **Heat capacity**
- **Magnetic permeability**
- **Martensite**
- **Metallurgy**
- **Ordontology**
- **Orthondoncy**
- **Ossification**
- **psi**
- **Rigidity**
- **Rockwell hardness**
- **Root analog**
- **Stainless steel**
- **Stiffness**
- **Tension**
- **Tetragonal**
- **Tetragonal FCC system**
- **Titanium**
- **Titanium powder**
- **Yield strength**

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APPENDIX I MECHANICS OF ORTHODONTICS.

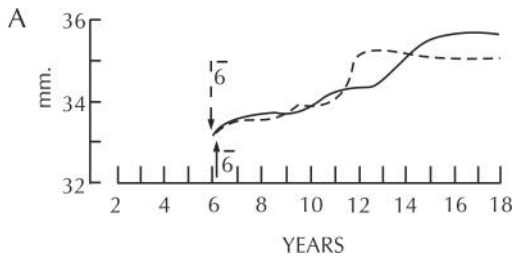


FIGURE 23 The stability of the mandible first permanent molar diameter (31).

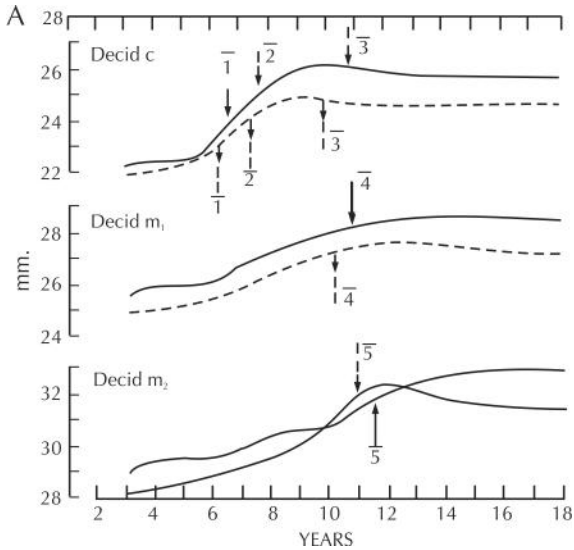


FIGURE 24 Changes in the diameters of mandible primary dental arch – Male (31).

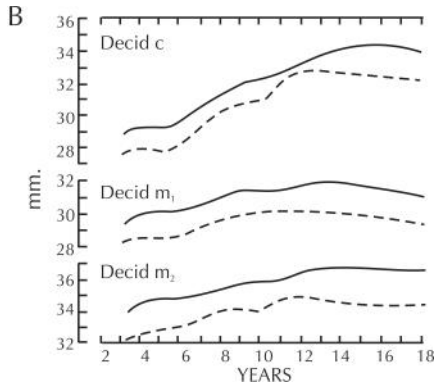


FIGURE 25 Changes in the diameters of mandible primary dental arch – Female (31).

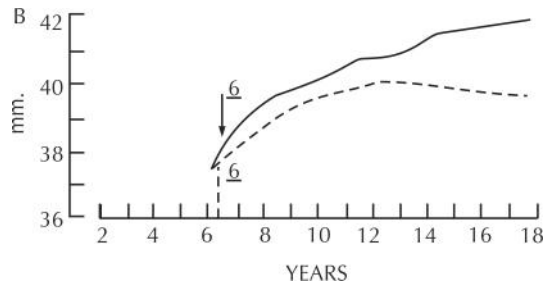


FIGURE 26 Width increases in the maxillary first permanent molar region (31).

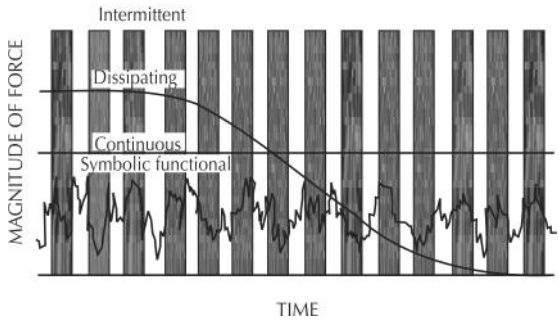


FIGURE 27 Schematic presentation of manner of orthodontic force application (31).

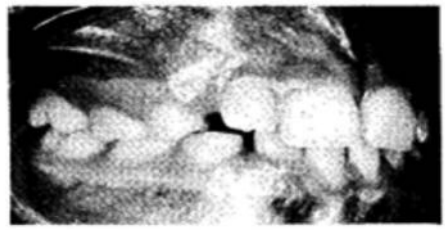


FIGURE 28 Example of arborization applied to actual cases. (31).

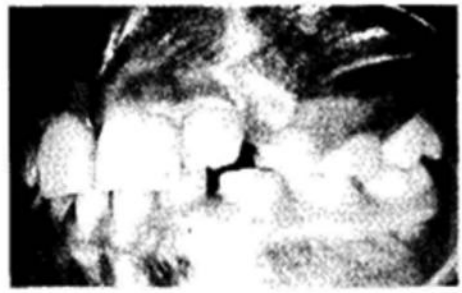
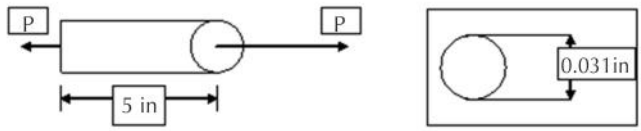


FIGURE 29 Example of arborization applied to actual cases. (31).

APPENDIX II: NUMERICAL EXERCISES.

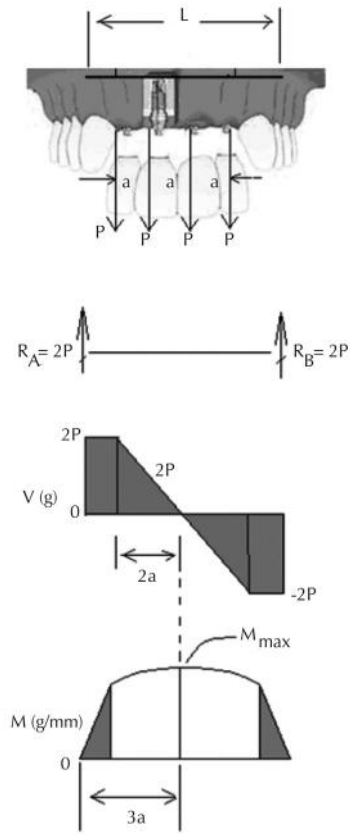
Example 1. A braces wire is used in tension to press the teeth to put it in place. If the wire has a diameter of 0.8 mm or 0.031 in; initial length, Lo = 5 inches; normal strain, $\epsilon = 500e^{-6}$; and normal stress, $\sigma = 3$ ksi = 3000 psi.



Find the elongation of the wire:
$\epsilon = \delta/Lo$
$\delta = \epsilon * Lo$
$\delta = (500\ e^{-6}) * (5\ in) = 0.0025$ inches
Therefore, the final length:
$L = Lo + \delta = 5\ in + 0.0025\ in = 5.0025$ inches

Find the load, P:
$\sigma = P/A$ or $P = \sigma A$
$P = (3000\ lb/in^2) * (\pi/4\ D^2) = (3000\ lb/in^2) * (\pi/4\ (0.031^2))$
$P = (3000\ lb/in^2) * (0.000755\ in^2)$
$P = 2.2643$ lb

Example 2. Draw the shear-force and bending moment diagrams for the teeth support and the teeth loads.



GLOSSARY OF TECHNICAL TERMS

Abdominal aorta – The portion of the aorta in the abdomen.

Abdominal ultrasound – a diagnostic imaging technique which creates images from the rebound of high frequency sound waves in the internal organs.

Abdominal x-ray – a simple study that will give the physician an idea of how the internal organs look.

Ablution – act of washing or bathing.

Abruptio placenta is a retro placental blood clot formation, abnormal hemorrhage prior to delivery.

Absces – it is a bacterial infection that may be introduced from the bloodstream in cases of generalized or distant infection or form contiguous infection following a skull fracture.

Absorption – The movement of nutrients and other substances through the wall of the digestive tract and into the blood.

Acclimatization – Physiological changes, which occur in response to several days of heat exposure and make the body accustomed to a hot environment.

Accommodation – Adaptation by the sensory receptors to various stimuli over an extended period of time.

Acoustic-spectrum – The range of frequencies and wavelengths of sound waves.

Action potential – A recorded change in electrical potential between the inside and outside of a nerve cell, resulting in muscular contraction.

Active electrode – Electrode at which greatest current density occurs.

Active Transport – A not completely understood process occurs in several critical locations in living systems. This process results in a species being transferred across a membrane against a concentration gradient, that is, "up the concentration hill." We realize in light of free-energy considerations that such a process must be supplied energy from an external source in order to operate.

Acute – severe; sharp; begins quickly.

Adrenal cortex – The outer region of each adrenal gland; secretes steroid hormones.

Adrenal glands – Paired endocrine glands, one located just superior to each kidney.

Afferent – Conduction of a nerve impulse toward an organ.

AFI – Amniotic Fluid Index.

Allantois – An extraembryonic membrane, endoderm in origin extension from the early hindgut, then cloaca into the connecting stalk of placental animals, connected to the superior end of developing bladder. In reptiles and birds, acts as a reservoir for wastes and mediates gas exchange. In mammals is associated/incorporated with connecting stalk/placental cord fetal-maternal interface.

Allergy – a condition in which the body is not able to tolerate eating certain foods, or exposure to certain animals, plants, or other substances.

Alveoli – Air sacs in the lungs where oxygen and carbon dioxide are exchanged.

Alveolus – An air sac of the lung through which the gas exchange with the blood takes place.

Amnion – Membrane located inside amniotic cavity, composed of ectodermal cells that cover the inner surface of the amniotic

Amniotic fluid – The fluid which, contained in the sac of membranes known as the amnion, surrounds the fetus and provides a shock absorber and a secondary vehicle for the exchange of body chemicals with the mother.

Amniotic sac – Amniotic sac is a thin-walled sac that surrounds the fetus during pregnancy. The sac is filled with amniotic fluid (liquid made by the fetus) and the amnion (the membrane that covers the fetal side of the placenta), which protects the fetus from injury and helps to regulate the temperature of the fetus.

Amplitude – The intensity of current flow as indicated by the height of the waveform from baseline.

Amylase – Enzyme, also called diastase. It is found in both plants and animals.

Anal fissure – a small tear in the anus that can cause bleeding, itching, or pain.

Analgesia – Loss of sensibility to pain.

Analgesic – any drug intended to alleviate pain.

Anastomosing – connecting the end of an artery with a similar vessel; end-to-end

Anastomosis is used to describe the connection between peripheral blood vessels without an intervening capillary bed.

Anemia – not enough red blood cells in the body.

Anesthesia – Loss of sensation.

Aneurysm – bulge in the blood vessel; affect the large arteries throughout the body.

Angina – chest pain.

Angiogenesis describes the development of new vessels from already existing vessels. This process is secondary to vasculogenesis which is the initial formation of first blood vessels by differentiation of pluripotent mesenchymal cells (extraembryonic mesoderm).

Angiography – An x-ray technique that makes use of a dye injected into the coronary arteries to study blood circulation through the vessels. The test allows physicians to measure the degrees of obstruction to blood flow. Circulation through an artery is not seriously reduced until the inside diameter of the vessel is more than 75% obstructed.

Angioplasty – A nonsurgical technique for treating diseased arteries by temporarily inflating a tiny balloon inside an artery.

Angiotensins – are a group of hormones that are powerful vaconstrictors.

Anode – Positively charged electrode in a direct cur rent system.

Anorectal atresia – absence of a normal opening between the anus and the rectum.

Antacids – medicines that neutralize stomach acid.

Anterior choroidal artery – Anterior choroidal artery usually arises from the ICA just beyond the origin of the PoCA.

Anticholinergics – medicines that help calm spasms in the intestine.

Anticoagulant – Any drug that keeps blood from clotting; a blood thinner.

Antidiarrheals – medicines that help control diarrhea.

Antiemetics – medicines that help prevent and control nausea and vomiting.

Antispasmodics – medicines that help reduce or stop muscle spasms in the intestines.

Anus – opening at the end of the digestive tract where bowel contents leave the body.

Aorta – The largest and main systemic artery of the body; arises from the left ventricle and branches to distribute blood to all parts of the body except the lungs. A blood vessel that delivers oxygen-rich blood from the left ventricle to the body; it is the largest blood vessel in the body.

Aortic valve – The valve that regulates blood flow from the heart into the aorta. Outlet valve from left ventricle to aorta.

Apex – top portion of the upper lobes of the lungs.

Appendectomy – an operation to remove the appendix.

Appendicitis – irritation, inflammation, and pain in the appendix, caused by infection, scarring, or obstruction (blockage).

Appendix – a small pouch attached to the first portion of the large intestine (the cecum); it has no known function.

Applicator- The electrode used to transfer energy in microwave diathermy.

Arrhythmia: An alteration in rhythm of the heartbeat either in time or force.

Arterioles – Small, muscular branches of arteries. When they contract, they increase resistance to blood flow, and blood pressure in the arteries increases.

Artery – A vessel that carries oxygen-rich blood to the body.

Artery, Anterior Cerebral – it passes anteromedially via the horizontal plane to enter the inter-heimispheric fissure, anastomoses with the contralateral ACA via the anterior communicating artery forming the anterior portion of the circle of Willis.

Artery, Anterior choroidal – it originates occasionally from the PoCA or the middle cerebral artery (MCA).

Artery, External Carotid – is the artery that supplies blood to the jaw, face, neck and meninges.

Artery, Internal Carotid – it starts at the carotid sinus at bifurcation of CCA (Common Carotid Artery) at the level of the upper border of the thyroid cartilage al the level of the fourth cervical vertebra.

Artery, Middle Cerebral – it is the largest branch of ICA and appears almost as its direct continuation.

Artery, Ophthalmic – it passes through the optic canal to supply the eye and other structures of the orbit.

Artery, Posterior Cerebral (PCA) – the basilar artery ends by dividing into the two posterior cerebral arteries.

Artery, Posterior Communication – it arises just before the termination of the ICA and passes backward to the join the first part of the posterior cerebral artery PCA.

Arthritis – Arthritis is one of the most pervasive diseases in the United States and is the leading cause of disability.

Ascending colon – the portion of the large intestine that is on the right side of the abdomen.

Ascites – fluid that fills the abdomen when the liver is not functioning properly.

Atherosclerosis – A form of arteriosclerosis, is the reduction in blood flow through the arteries caused by greasy deposits called plaque that form on the insides of arteries and partially restrict the flow of blood.

Atonic colon – lack of normal muscle strength in the large intestine; caused by overuse of laxatives or by a disease called Hirschsprung's disease.

Atonic – Without tone.

Atresia – lack of a normal opening, from the esophagus, the intestines, or the anus.

Atria – The two upper or holding chambers of the heart.

Atrioventicular valve – a valve between each atrium and its ventricle that prevents back flow of blood. The right trioventricular valve is the tricuspid valve; the left atrioventricular valve is the mitral valve.

Atrioventricular node – mass of specialized cardiac tissues that receive and impulse from sinoatrial node (peacemaker) and conducts it to the ventricles.

Atrium – An anatomical cavity or passage; especially a main chamber of the heart into which blood returns from circulation.

Axial Pump – Rotary pump with axial flow

Axilla – The cavity beneath the junction of the arm and the body, better known as the armpit.

Backflow – flow of blood backward through the heart

Balloon urethroplasty – a thin tube with a balloon is inserted into the opening of the penis and guided to the narrowed portion of the urethra, where the balloon is inflated to widen the urethra and ease the flow of urine.

Barium – a liquid used to coat the inside of organs so they will show up on an x-ray.

Barium enema – a procedure done to evaluate the large intestine for abnormalities. A fluid called barium that shows up well on x-rays is given into the rectum as an enema. An x-ray of the abdomen shows strictures (narrowed areas), obstructions (blockages), and other problems.

Barrett's esophagus – A condition in which normal cells that line the esophagus, called squamous cells, turn into abnormal cells, called specialized columnar cells. Damage to the lining of the esophagus causes the cells to change; often occurs with long-term acid reflux.

Basal cells – Are more or less rounded cells located to the basal lamina. They partly sheathe the first portion of the axon of the olfactory cell that extends from the epithelium to the underlying connective tissue.

Base – bottom portion of lower lobes, located just above the diaphragm.

Benign prostatic hyperplasia (Also called BPH or Benign prostatic hypertrophy) – an enlargement of the prostate caused by disease or inflammation. It is not cancer, but its symptoms are often similar to those of prostate cancer.

Benign Tumors – abnormalities on the neuroglia cells.

Bicuspid aortic valve – The aortic valve normally has three leaflets or cusps. Occasionally an individual is born with a valve having only two cusps – called a bicuspid valve.

Bile – a digestive fluid made by the liver and stored in the gallbladder which helps digest fats.

Bile ducts – tubes that take bile from the liver to the gallbladder and small intestine to aid in digestion.

Biliary atresia – bile ducts do not have normal openings, preventing bile from leaving the liver. This causes jaundice (a yellow skin color) and liver damage known as cirrhosis. Biliary atresia is a birth defect.

Bilirubin – a normal substance produced when red blood cells break down and are excreted by the liver. Bilirubin gives bile its yellow-green color. Too much bilirubin in the blood causes jaundice.

Bioengineering – is the application of engineering knowledge to the fields of medicine and biology.

Bioheat Transfer – The human body is composed of 70% of fluids which help in the thermo-regulatory processes for maintaining a constant temperature of 37.4°C.

Biological valves – Artificial valves made from humans or animals, rather than from metal, are called biological valves. Examples of biological valves are porcinexenografts, human homografts or allografts, and pulmonary autografts.

Biopsy – a procedure in which tissue samples are removed (with a needle or during surgery) from the body for examination under a microscope; to determine if cancer or other abnormal cells are present.

Biot number (Bi) – is a dimensionless number used in unsteady-state and heat transfer calculations. It relates the heat transfer resistance inside and at the surface of a body.

Bladder – a triangle-shaped, hollow organ located in the lower abdomen that holds urine. It is held in place by ligaments that are attached to other organs and the pelvic bones. The bladder's walls relax and expand to store urine, and contract and flatten to empty urine through the urethra.

Bladder instillation (Also called a bladder wash or bath) – the bladder is filled with a solution that is held for varying periods of time, from a few seconds to 15 minutes, before being drained through a catheter.

Blood Brain Barrier – prevent materials from the blood from entering the brain.

Blood clot – A jelly-like mass of blood tissue formed by clotting factors in the blood. Clots stop the flow of blood from an injury; they can also form inside an artery whose walls are damaged by atherosclerotic build-up and can cause a heart attack or stroke.

Blood filters – inserted into arterial line to remove gas and particulate emboli.

Blood pressure – The force exerted by blood against the inner walls of the blood vessel.

Blood – A fluid, circulating connective tissue that transport nutrients and others materials through the body.

Body fluid, **bodily fluids** or **biofluids** are liquids originating from inside the bodies of living people. **Body fluid** is a term most often used in medical and health contexts. Modern medical, public health, and personal hygiene practices treat body fluids as potentially unclean. This is because they can be vectors for infectious diseases, such as sexually transmitted diseases or blood-borne diseases. Universal precautions and safer sex practices try to avoid exchanges of body fluids. Body fluids can be analyzed in medical laboratory in order to find microbes, inflammation, cancers, etc.

Body temperature – Body Temperature, degree of body heat in cold- and warm-blooded animals.

Body water is water content of the human body. They include fluids that are excreted or secreted from the body as well as body water that normally is not.

Bowel – small and large intestine.

Bowel movement – passage of stool (body wastes) from the large intestine through the rectum and anus.

Bowman's capsule – Doubled wall sac of cells that surrounds the glomerulus of each nephron.

Brachial -relating to the arm or a comparable process.

Brain – Concentration of nerve tissue in the front or upper end of an animal's body.

Brain stem – The part of the brain that includes the medulla, pons, midbrain, thalamus and hypothalamus.

Bronchiole – Air duct in the lung that branches from a bronchus; divides to form air sacs Alveoli).

Bronchiolitis – inflammation that involves the bronchioles (small airways).

Bronchoscopy – a fiberoptic, flexible tube is passed through the mouth into the bronchi to locate tumors or blockages, and to gather samples of tissue and/or fluid.

Bronchus – large airways; lung divides into right and left bronchi.

Bronchus – One of the branches of the trachea and its immediate branches within the lung.

BTR – Bridge to Recovery: medical indication aiming not at a heart transplant, but at the recovery of the heart.

BTT – Bridge to Transplantation: medical indication referring to the bridging of the waiting period before a heart transplant.

Bubble oxygenator – injects oxygen directly through a column of blood; direct blood-gas interface exists; and gas bubbles are formed that must be removed in defoaming section; traumatic to blood elements; contributes to protein denaturation and formation of microemboli.

Buffer – A compound that stabilizes the pH of a solution by removing or releasing hydrogen ions.

Bulk degradation – Degradation occurs throughout the polymer structure in a rather random fashion.

Bundle of his – A small band of cardiac muscle fibers transmitting the waves of depolarization from the atria to the ventricles during cardiac contraction.

Cable electrodes- An inductance type electrode in which the electrodes are coiled around a body part creating an electromagnetic field.

Candida – yeast that causes irritation and infection, especially of the mucous membranes of the body such as the mouth, vagina, and anus.

Cannula – a tube designed for insertion into a duct, body cavity, or blood vessel. The rigid or semi-rigid structure of the cannula can be used as an introducer to insert an endocardial lead into the venous system.

Capillaries – Microscope blood vessels in the tissues the permit exchange of materials between cells and blood.

Carbohydrates – one of three main types of foods, along with proteins and fats. Found in breads, cereals, grains, fruits, and vegetables. Changed into a simple sugar called glucose during digestion. Provides the body with a source of energy.

Cardiac – Pertaining to the heart

Cardiac arrest – Standstill of the heart, its action and diseases.

Cardiac cycle – One complete heart beat.

Cardiac output – The amount of blood the heart pumps through the circulatory system in one minute.

Cardiology – The study of the heart, its action and diseases.

Cardioplegia – paralysis of the heart.

Cardioplegia Infusion – used to cool and deliver cardioplegia solution; uses a separate roller head; when blood cardioplegia is used, system is connected to arterial blood supply.

Cardiotomy Suction – suction used to aspirate blood from operative site and return to cardiotomy reservoir.

Cardiovascular (CV) – Pertaining to the heart and blood vessels. The circulatory system of the heart and blood vessels is the cardiovascular system.

Cardiovascular disease – Diseases of the heart or blood vessels.

Carpal tunnel syndrome – A painful and disabling disorder characterized by inflammation and swelling in the tendons that run through the narrow carpal tunnel in the wrist, and one of the most common of repetitive motion injuries.

Catheter – A narrow tube, which can be passed inside blood vessels to the heart for diagnostic and treatment purposes.

Cathode- Negatively charged electrode in a direct current system.

Cecum – the beginning of the large intestine. Attached to the last section of the small intestine, known as the ileum.

Central Nervous System (CNS) – The brain and spinal cord.

Centrifugal pump – transforms potential energy generated by electromagnetic forces into kinetic energy; vortex principle.

Cephalic – Of or relating to the head.

Cerebellum – A convoluted subdivision of the brain concerned with the coordination of muscular movements, muscle tone, and balance.

Cerebral Cortex – Layer of gray matter that constitutes the outer layer of the cerebrum and is responsible for integrating sensory impulses and for higher intellectual functions.

Cerebral Perfusion Pressure – is defined as the difference between mean arterial and intracranial pressure.

Cerebrospinal fluid (CSF) – Clear, colorless liquid that surrounds the brain and spinal cord and fills the spaces; and that bathes the central nervous system.

Cerebrum – Large, convoluted subdivision of the brain; it functions as the center for learning, voluntary movement, and interpretation of sensation.

Cervix is a lower part of the uterus that projects into the vagina. Made up of mostly fibrous tissue and muscle, the cervix is circular in shape.

Chiari Malformation – extra cerebellum crowdings the outlet of the brainstem/spinal cord from the skull on its way to the spinal canal.

Cholangiography – x-rays of the bile ducts.

Cholecystectomy – an operation to remove the gallbladder.

Cholesterol – a substance normally made by the body, but also found in foods from animal sources, like beef, eggs, and butter. Too much cholesterol in the body can lead to narrowing and blockage of the arteries, especially those that feed the heart and keep it healthy. High cholesterol can also cause the formation of gallstones. Ideally, blood cholesterol levels should be less than 200mg/dL.

Chorioamnionitis (CA) **–** An intraamniotic puerperal infection described as having 3 forms: histologic, clinical (clinical chorioamnionitis, IAI), and subclinical. Intraamniotic infection is a common (2-4%) event in labor and the systemic inflammatory response can also lead to preterm birth and neonatal complications.

Chorion is an extraembryonic membrane generated from trophoblast and extraembryonic mesoderm that forms placenta. Chorion and amnion are made by the somatopleure. The chorion becomes incorporated into placental development. The avian and reptilian chorion lies beside the egg shell and allows gas exchange.

Chorion frondosum (*frondosum* = leafy) **–** The chorion found on conceptus oriented towards maternal blood supply where the majority of villi form and proliferate, will contribute the fetal component of the future placenta.

Chorion laeve (*laeve* = smooth) **–** The smooth chorion found on conceptus away from maternal blood supply (towards uterine epithelium and cavity) with very few villi present.

Chorionic cavity – The fluid-filled extraembryonic coelom (cavity) formed initially from trophoblast and extraembryonic mesoderm that forms placenta, chorion and amnion are made by the somatopleure. The chorion becomes incorporated into placental development. The avian and reptilian chorion lies beside the egg shell and allows gas exchange. In humans, this cavity is lost during week 8 when the amniotic cavity expands and fuses with the chorion.

Chorionic somatomammotropin (CSH, human lactogen) **–** A hormone synthesized within the placenta by syncytiotrophoblast cells. This protein hormone (190 amino acid) has a structure similar to pituitary growth hormone.

Chorionic villus sampling (CVS) **–** The taking a biopsy of the placenta, usually at the end of the second month of pregnancy, to test the fetus for genetic abnormalities.

Chronic – referring to a disease or disorder that usually develops slowly and lasts for a long period of time.

Chyme – The semifluid mass of partly digested food expelled by the stomach into the duodenum.

Circuit- The path of current from a generating source through the various components back to the generating source.

Circulatory system: The body system that functions in internal transport and protects the body from disease.

Cirrhosis – a chronic problem makes it hard for the liver to remove toxins (poisonous substances) from the body. Alcohol, medications, and other substances may build up in the bloodstream and cause problems. Cirrhosis is a result of scarring and damage from other diseases, like biliary atresia and alcoholism.

Clitoris – A small, erectile structure at the anterior part of the vulva in females; homologous to the male penis.

Clostridium difficile (Also known as C. diff or C. difficile.) – bacteria normally found in the large intestine, which can cause a serious intestinal infection and diarrhea in some people who are taking antibiotics.

Coaxial cable – Heavy, well-insulated electrical wire.

Cochlea – The structure of the inner ear that contains the auditory receptors (organ of Corti).

Coelocentesis – A sampling of extracoelomic fluid usually for an early prenatal diagnostic technique.

Cold-induced vasodilatation – Vasodilatation following cold application.

Colic – a condition in an otherwise healthy baby characterized by excessive crying.

Colitis – irritation of the colon (large intestine).

Collagen tissue- Fibrous insoluble protein found in connective tissue, bone, ligaments, and cartilage.

Collecting duct – A duct in the kidney that receives filtrate from several nephrones and conducts it to the renal pelvis.

Colloid – The fluid suspension of the body's intercellular fluid.

Colon – Portion of the large intestine between the cecum and the rectum.

Common bile duct – a tube that moves bile from the liver to the small intestine.

Computed tomography scan (Also called a CT or CAT scan) – a diagnostic imaging procedure that uses a combination of x-rays and computer technology to produce cross-sectional images (often called slices), both horizontally and vertically, of the body. A CT scan shows detailed images of any part of the body, including the bones, muscles, fat, and organs. CT scans are more detailed than general x-rays.

Condenser electrodes – An electrical current is con ducted back and forth between the two electrodes. Highest concentration is under the electrodes, which may be pads or space plates. Highest concentration is also in fat tissue

Conduction – This is the only method of heat transfer in opaque solids. If the temperature at one end of a metal rod is raised by heating, heat is conducted to the colder end, but the exact mechanism of heat conduction in solids is not entirely_understood.

Congestion – Presence of an abnormal amount of blood in the vessels as a result of an increase in blood flow or obstructed venous return.

Consensual heat vasodilatation – Increased blood flow that spreads to a remote area of the body as a result of localized heating.

Constipation – hard, dry stools that are difficult to pass in a bowel movement, or having fewer than three bowel movements per week.

Contrast bath – Hot (106° F) and cold (50° F) treatments in a combined sequence to stimulate superficial capillary vasodilatation or vasoconstriction.

Coronary arteries – Two arteries arising from the aorta that arch down over the top of the heart and divide into branches. They provide blood to the heart muscle.

Coronary artery and sinus – Vessels carrying blood to and from the walls of the heart itself.

Corpus collosum – A large bundle of nerve fiber interconnecting the two cerebral hemispheres.

Corpus luteum – The temporary endocrine tissue in the ovary that develops from the ruptured follicle after ovulation.

Cortical – Relating to, or consisting of the cortex.

Corticosteroids – medications that reduce irritation and inflammation.

Coupling agent- A substance used as a medium for the transfer of sound waves.

CPB – cardiopulmonary bypass.

Cranial nerves – Ten to twelve pairs of nerves that emerge directly from the brain.

Craniocerebral Trauma – can cause bleeding into the brain.

Crohn's disease – A chronic illness that causes irritation in the digestive tract. It occurs most commonly in the ileum (lower small intestine) or in the colon (large intestine). It is a form of inflammatory bowel disease.

Cryokinetics – The use of cold and exercise in the treatment of pathology or disease.

Cryotherapy – The use of cold in the treatment of pathology or disease.

Crystal – The part of the ultrasound head that vibrates and changes shape.

Cyanosis – bluish color in the skin because of insufficient oxygen.

Cystoscopy (Also called cystourethroscopy) – an examination in which a scope, a flexible tube and viewing device, is inserted through the urethra to examine the bladder and urinary tract for structural abnormalities or obstructions, such as tumors or stones.

Cystourethrogram (Also called a voiding cystogram) – a specific x-ray that examines the urinary tract. A catheter (hollow tube) is placed in the urethra (tube that drains urine from the bladder to the outside of the body) and the bladder is filled with a liquid dye. X-ray images will be taken as the bladder fills and empties. The images will show if there is any reverse flow of urine into the ureters and kidneys.

Cytotrophoblast can invade the maternal decidua, form columns to attach villi, or fuse to form syncitiotrophoblast cells. Beginning at uterine adplantation, proliferation and fusion of these cells is thought to form a second outer trophoblast layer, the syncytiotrophoblast. The cytotrophoblast layer contributes to formation of the placental villi, the functional component of the fetal placenta.

Decidua basalis is a term given to the uterine endometrium at the site of implantation where signaling transforms the uterine stromal cells (fibroblast-like) into decidual cells. This forms the maternal component of the placenta, the decidualization process gradually spreads through the remainder of the uterus, forming the decidua parietalis.

Decidua basalis reaction is a term describing the maternal endometrial changes that occur initially at the site of, and following, blastocyst implantation. It is seen as a deposition of glycogen, fibrin and proliferation of blood vessels.

Decidua capsularis is a term given to the uterine endometrium which has been converted to decidua surrounding the conceptus on the smooth chorion side.

Decidua parietalis is a term given to the remainder of the uterine endometrium, away from the site of implantation, that gradually becomes converted to decidua.

Decidual cell – The uterine stromal cells (fibroblast-like) that differentiate in response to both steroid hormones (progesterone) and embryonic signals. These cells then alter uterine environment to support further embryonic development as well as producing cytokines related to prolactin (PRL) and have an innate immune function.

Decidualization (decidualisation) is a process by which uterine stromal cells differentiate in response to both steroid hormones and embryonic signals into large epitheliod decidual cells. This process is essential for the progress of implantation and establishing fetal-maternal communication.

Deep vein thrombosis – A blood clot in the deep vein in the calf.

Dehydration is a loss of body water component of body fluid: when the bloodstream and the cells of the body contain less fluid than normal, often due to vomiting or diarrhea.

Dendrite – A branch of a neuron that receives and conducts nerve impulses toward the cell body.

Dendrites – a cell body with branching structures that receive impulse from neurons and transmit them to the cell body of the neuron in which these are embedded.

Depolarization – Process or act of neutralizing the cell membrane's resting potential.

Dermis – The layer of dense connective tissue beneath the epidermis in the skin of vertebrates.

Descending colon – the portion of the large intestine located on the left side of the body.

Dialysis – a medical procedure to remove wastes and additional fluid from the blood after the kidneys have stopped functioning.

Diaphragm – The diaphragm is the primary muscle of inspiration. It is a thin, dome-shaped sheet of muscle that inserts into the lower ribs. When it contracts, it pushes downward and spreads out, increasing the vertical dimension of the chest cavity and driving up abdominal pressure. This increase in pressure drives the abdominal contents down and out, which in turn increases the transverse size of the chest cavity.

Diarrhea – increase in frequency of stools compared to normal, or looser bowel movements than usual. Causes include infections of the digestive system, medicines such as antibiotics, malabsorption, and irritable bowel syndrome.

Diastole – Phase of the cardiac cycle in which the heart is relaxed.

Diastolic pressure – lowest pressure to which blood pressure falls between contractions of the ventricles.

Diathermy – The application of high-frequency electrical energy that is used to generate heat in body tissues as a result of the resistance of the tissue to the passage of energy.

Diffuse Axonal Injury – after a closed brain injury, the shifting and rotation of the brain inside the skull will result in shearing injury to the brain's long connecting nerve fibers or axons.

Diffusion – The natural tendency of molecules to move out of areas of high concentration into areas of low concentration until a solution or gas has a uniform concentration of the molecules.

Diffusion system – the drug is either encapsulated in a polymer membrane or suspended within a polymer matrix; water diffuses into the membrane or matrix, the drug dissolves, and finally the dissolved drug diffuses out of the polymer.

Digestion – how the body breaks down food and uses it for energy, cell repair, and growth. Starts in the mouth, continues in the stomach and small intestine, and is completed in the large intestine. The liver and pancreas add enzymes and juices that aid in this process.

Digestive tract – the organs that are involved in digestion; including the mouth, salivary glands, esophagus, stomach, pancreas, liver, gallbladder, small intestine, and large intestine.

Digital rectal exam (DRE) – a procedure in which the physician inserts a gloved finger into the rectum to examine the rectum and the prostate gland for signs of cancer.

Dilate – relax; expand.

Dimensionless number – is a quantity which describes a certain physical system and which is a pure number without any physical units. Such a number is typically defined as a product or ratio of quantities which do have units, in such a way that all units cancel. For example: *"one*

out of every 10 apples I gather is rotten." The rotten-to-gathered ratio is *[1 apple] / [10 apples] = 0.1*, which is a dimensionless quantity .Dimensionless numbers are widely applied in the field of mechanical and chemical engineering. According to the Buckingham π-theorem of dimensional analysis, the functional dependence between a certain number (e.g., n) of variables can be reduced by the number (e.g., k) of independent dimensions occurring in those variables to give a set of $p = n - k$ independent, dimensionless numbers. For the purposes of the experimenter, different systems which share the same description by dimensionless numbers are equivalent.

Direct current – Galvanic current that always flows in the same direction and may flow in either a positive or a negative direction.

Distention – swelling or bloating, usually referring to the abdomen.

Diverticulitis – occurs when one or more small pouches in the large intestine (called a diverticulum) become irritated or infected.

Diverticulum – a small pouch in the wall of the large intestine, which usually do not cause a problem unless it becomes irritated

Donor – an organism that supplies living tissue to be used in another body, as a person who furnishes organ transplantation or blood transfusion

Douche – A current of water directed against the skin surface (e.g., scotch douche alternating hot and cold water).

Ductus arteriosus – A vascular connection between the pulomonary trunk and aorta that functions throughout the fetus.

Ductus venosus -A vessel that allows the blood to bypass the liver.

Duodenal ulcer – an open sore in the duodenum (first part of the small intestine).

Duodenum – The portion of the small intestine into which the contents of the stomach first enter.

Dysphagia – difficulty swallowing food or liquid.

Dyspnea – sensation of difficulty in breathing.

Eccrine sweat glands – They are distributed over the entire surface of the body except at a relatively few locations such as the lips and external genitalia.

ECG – Abbreviation for electrocardiogram.

Echocardiogram – An ultrasonic record of the dimension and movement of the hearts and his valves.

Edema – swelling due to the buildup of fluid.

EEG – Abbreviation for electroencephalogram.

Electrical field – A technique of heating the tissues in shortwave diathermy in which the patient is part of the electrical circuit.

Electrical potential – The difference between charged particles at a higher and lower potential.

Electrocardiogram (EKG) – The electrocardiogram is a graph that indicates electrical impulses flow through the heart. Abnormalities may indicate that a heart attack has occurred in the past. If performed during symptoms suggestive of coronary artery disease angina pectoris, abnormalities may confirm the diagnosis of ischemic heart.

Electrocardiogram – A record of the electric activity of the heart.

Electrocardiograph – An instrument used for the measurement of the electrical activity of the heart.

Electroencephalogram (EEG) – a procedure that records the brain's continuous electrical activity by means of electrodes attached to the scalp.

Electroencephalograph – An instrument for measuring and recording electrical activities from the brain (brain waves).

Electrolytes – minerals in the bloodstream and in the cells of the body, such as sodium (salt), potassium, and calcium. Electrolytes must remain in proper balance for the body to function normally.

Electromagnetic spectrum – The range of frequencies and wavelengths associated with radiant energy.

Electromyography – The pick-up and amplification of electrical signals generated by the muscle as it contracts.

Electroporation – Is a widely used method of punching multiple holes in the cell membrane.

Electrostatic or condenser field – The patient is placed between electrodes and becomes a part of a series circuit.

Encopresis – constipation and intestinal obstruction (blockage) lead to an involuntary leakage of loose stool.

Endocrine glands – They produce hormones and secrete them into the surrounding tissue fluid, from which they diffuse into capillaries. Hormones are then transported through the body by the blood but elicit responses only in their target tissues.

Endocrine system – Body system that helps regulate metabolic activities; consists of ductless glands and tissues that secretes hormones.

Endorphins – Endogenous opiates whose actions have analgesic properties. They are neurophor mones and not neurotransrnitters (i.e., β-endor- phins).

Endoscope – a small, flexible tube with a light and a camera lens at the end, used to examine the inside of the digestive tract. It can also be used to take tissue samples for testing from inside the digestive tract.

Endoscopy – a test that uses an endoscope to examine the inside of part of the digestive tract.

Endothelial cells – the delicate lining, only one cell thick, of the organs of circulation.

Endothelium – the cells or membrane lining organs.

Endovascular trophoblast migrates into the maternal spiral arteries.

Enema – a liquid placed into the rectum to either clear stool out of the large intestine, or to examine the large intestine with an x-ray (barium enema).

Enkephalin – Neurotransmitter proteins that are pain-relieving molecules. They block the passage of noxious stimuli by servicing descending neurons to counter ascending signals. They inhibit the release of substance P and are produced by enkephalinergic neurons.

Enkephalinergic neurons – Neurons with short axons that release enkephalin. They act as interneUrofls (internuncial neurons) and are found in the substantia gelatinosa, nucleus raphae magnus, and periaqueductal gray matter.

Enteral Route – It concerns the absorption via one or more of the following components of the GI tract: the buccal cavity and sublingually, gastrically, intestinally, and rectally.

Enuresis – involuntary discharge of urine usually during sleep at night; bedwetting beyond the age when bladder control should have been established.

Enzyme – A protein that speeds up chemical reactions in the body. (CNet) Any of a group of chemical substances which are produced by living cells and which cause particular chemical reactions to happen while not being changed themselves. E.g., an enzyme in the saliva of the mouth starts the process of breaking down the food.

Enzyme Linked Immunosorbent Assay (ELISA) – A blood test used to detect bacteria that can cause ulcers known as Helicobacter pylori (or H. pylori).

Epidermis – It is a layer of stratified squamous epithelium. In thick skin, five layers can be discerned in the epidermis. Beginning with the deepest part of the epidermis and moving toward the surface, these are the stratum basale, the stratum spinosum, the stratum granulosum, the stratum lucidum and the stratum corneum.

Epididymis -A coiled duct that connects the rete testis to the ductus deferens; site of functional maturation of spermatozoa.

Epiglottis – A thin, flexible structure that guards the entrance to the larynx, preventing food from entering the airway during swallowing.

Epinephrine – Hormone produced by the adrenal gland.

Epithelium – the cells or membrane covering the outside of organs.

Escherichia coli (Also known as E. coli) – A bacteria that can cause infection of the large intestine. E. coli is found in rare or undercooked meat, and can also be spread by using dirty cooking utensils or through contaminated water.

Esophageal atresia – during pregnancy, the baby's esophagus does not develop properly, and ends before reaching the stomach. Food cannot pass from the mouth into the stomach.

Esophageal manometry – a test that measures the muscle tone in the esophagus.

Esophageal pH monitoring – a test used to monitor the amount of acid in the esophagus, which helps evaluate gastroesophageal reflux disease (GERD).

Esophageal stricture – a narrowing in the esophagus, often caused by irritation from long-term presence of acid in the esophagus with chronic gastroesophageal reflux disease (GERD).

Esophagogastroduodenoscopy (EGD) – a test using an endoscope to look at the inside of the esophagus, stomach, and upper part of the small intestine. Tissue samples can also be taken to test for diseases.

Esophagus – the tube that connects the mouth to the stomach.

Estrogen replacement therapy (ERT) – use of the female hormone estrogen to replace that which the body no longer produces naturally after medical or surgical menopause.

Euvolemia is the state of normal body fluid volume.

Excretion – The discharge from the body from a waste product of metabolism (Do not confuse with the elimination of undigested food materials).

Exocrine gland – Gland that excretes its product through a duct that opens onto a free surface.

Expiration – exhaling; giving off carbon dioxide.

Expiratory Reserve Volume – Volume that can be exhaled during forced breathing in addition to tidal volume—1100mL

External respiration – Movement of gases in and out of lungs.

External root sheath – It is the outermost part of the hair follicle.

Extracellular fluid – All body fluids other than that contained within the cells; includes plasma and interstitial fluid.

Extracorporeal – Lying outside the body

Extracorporeal shock wave lithotripsy (ESWL) – use of a machine to send shock waves directly to the kidney stone to break a large stone into smaller stones that will pass through the urinary system.

Facilitated diffusion – When the diffusion of a chemical species is accompanied by chemical reaction involving that species, the net rate of transport is often increased or "facilitated."

Fats – one of three main types of foods, along with proteins and carbohydrates. Provides the body with a source of energy. Needs bile in order to be digested properly and utilized for energy.

Fecal fat test – assesses how well the body can break down and absorb fat. A fat free diet is eaten for two to three days, and then stool samples are collected and examined for the amount of fat they contain.

Fecal occult blood test – checks for occult (hidden) blood in a random stool sample.

Fever – A fever is defined as a temperature 1° or more above the normal 98.6 degrees Fahrenheight (F) or 37 degrees Celsius (C).

Fiber – fiber is an ingredient in edible plants that aids in digestion. Fiber helps keep the stool soft, and keeps it traveling easily through the intestine. Fiber is found in vegetables, fruits, beans, and whole grains.

Fibrillation – apid, uncoordinated contractions of individual heart muscle fibers. The heart chamber involved can't contract all at once and pumps blood ineffectively, if at all

Fibrinogen – A plasma protein that is the soluble precursor of the fibrous protein fibrin.

Fibrinoid layer (Nitabuch's layer) is formed at maternal/fetal interface during placentation and is thought to prevent excessively deep conceptus implantation.

Fibrosis – process by which inflamed tissue becomes scarred.

Fistula – an abnormal connection between two organs, or between an organ and the outside of the body.

Fluid balance is the concept of human homeostasis that the amount of fluid lost from the body is equal to the amount of fluid taken in. The human homeostatic control mechanisms maintain a constant internal environment and ensure that a balance between fluid gain and fluid loss is maintained.

Fluid balance, negative – If fluid loss is greater than fluid gain (for example if the patient vomits and has diarrhea), the patient is said to be in negative fluid balance. In this case, fluid is often given intravenously to compensate for the loss.

Fluid balance, positive – If fluid loss is less than fluid gain, the patient is said to be in positive fluid balance that might suggest a problem with either the renal or cardiovascular system.

Fluid bonding refers to unprotected sex in long-term relationships. The relationships can be either monogamous or polyamorous. This is usually undertaken once medical advice and STI tests have been taken. By anecdotal accounts many couples who intend to become fluid bonded generally only do so when intending to undertake a serious exclusive relationship or even marriage; the method of choice being to undertake a pair of tests separated in time by one year, with either

complete abstinence or continuing to use condoms in the intervening time; a practice known as "double-gating". Properly used, "double-gating" will reduce the probability of either person in the couple having HIV to less than 1 in 10,000 if all tests turn up HIV-free. The one drawback to the approach is that this will not detect any cheating that may have been done a month or closer prior to the second set of tests, the maximum amount of time required for HIV to become detectable in the bloodstream, so this approach is not recommended for people who routinely have frequent partners. In polyamorous or open arrangements, there is usually an agreement to practice protected sex outside of those within the fluid bonded relationship(s).

Fluidotherapy- A modality of dry heat using a finely divided solid suspended in an air stream with the properties of liquid.

Fluoroscopy – Process of using an instrument to observe the internal structure of an opaque object (as the living body) by means of X rays.

Foramen ovale – Shunts a large portion of the incoming blood from the right atrium into the left atrium. When the baby is born, the foramen ovale closes, forming the separation of the heart into two pumps.

Forced expiratory flow – The average rate of flow for a specified portion of the forced expiratory volume, usually between 2E-4 and 0.0012 mm^3 (formerly called maximum expiratory flow rate).

Forced midexpiratory flow – The average rate of flow during the middle half of the forced expiratory volume.

Forced vital capacity – The maximum volume of gas that can be expelled as forcefully and rapidly as possible after maximum inspiration.

Frequency – The number of cycles or pulses per second.

Froude number – (named after William Froude) is the reciprocal of the square root of the Richardson number. The densimetric Froude number is usually preferred by modellers who wish to nondimensionalize a speed preference to the Richardson number which is more commonly encountered when considering stratified shear layers. For example, the leading edge of a gravity current moves with a front Froude number of about unity.

Functional incontinence – leakage of urine due to a difficulty reaching a restroom in time because of physical conditions such as arthritis.

Functional residual capacity – The volume of gas remaining in the lungs at the resisting expiratory level. The resting end-expiratory level is used as the baseline because it varies less than the end- inspiratory level.

Gallbladder – stores bile made by the liver; sends bile into the small intestine to help digest fats.

Gamma system- Nerve fibers that reset the muscle spindle to its adjusted length.

Ganglion – A mass of neuron cell bodies.

Gas – air that collects in the stomach and intestines as a natural result of digesting food. Passed out of the body via the rectum or the mouth.

Gastric – related to the stomach.

Gastritis – inflammation of the lining of the stomach.

Gastroenteritis – irritation or infection of the stomach and intestines. May be caused by bacteria or parasites, irritating food, stress, or emotional upset.

Gastroenterologist – a physician whose specialty is digestive diseases.

Gastroenterology – medical specialty that deals with the digestive system.

Gastroesophageal reflux disease (GERD) – movement of food, fluids, and digestive juices from the stomach back up into the esophagus; causes irritation of the esophagus with acid, resulting in discomfort. GERD occurs when the muscle between the stomach and the esophagus, known as the lower esophageal sphincter, opens when it should stay closed, or is weak.

Gastrointestinal tract (Also called the digestive tract) – An internal passageway that begins at the mouth, ends at the anus, and is lined by a mucous membrane; also called digestive tract. The parts of the body that break down food into small particles, allowing nutrients from food to be used for energy and growth: the mouth, esophagus, stomach, pancreas, liver, gallbladder, small intestine, and large intestine.

Gastroparesis – muscle or nerve damage in the stomach, which causes slow digestion and stomach emptying.

Gastrostomy – a surgically created opening in the stomach and the abdominal muscles. A tube is passed through these openings, into the stomach, to allow for feeding of a person who cannot eat normally.

GERD – gastroesophageal reflux disease.

Giardia lamblia – a parasite found in spoiled food or unclean water that can cause diarrhea.

Gland – See endocrine gland and exocrine gland.

Glial Cells – surround the neurons and help regulate the biochemical environment within the brain, provide structural supports for neurons and repaired the central nervous systems after injuries.

Glomerulonephritis – a type of glomerular kidney disease in which the kidneys' filters become inflamed and scarred, and slowly lose their ability to remove wastes and excess fluid from the blood to make urine.

Glomerulosclerosis – the term used to describe scarring that occurs within the kidneys in the small balls of tiny blood vessels called the glomeruli. The glomeruli assist the kidneys in filtering urine from the blood.

Glomerulus – The cluster of capillaries at the proximal end of the nephron; the glomerulus is surrounded by the Bowman's capsule.

Glucose – a simple sugar made by the body from carbohydrates in food. Glucose is the body's main source of energy.

Gluten – a protein in grains such as wheat, oats, rye, and barley.

Good pasture syndrome – A rare, autoimmune disease that can affect the lungs and kidneys.

Gray matter: Nervous tissue in the brain and spinal cord that contains the cell bodies, dendrite, and unmyelinated axons.

Ground- A wire that makes an electrical connection with the earth.

H2 blockers – Medications used to treat gastroesophageal reflux disease (GERD) that decrease the amount of acid made by the stomach. The stomach lining has sites that react to a chemical normally found in the body called histamine. When histamine attaches to these sites, the stom-

ach produces acid that aids in digestion of food. H2 blockers prevent the stomach from reacting to histamine, thereby decreasing stomach acid.

Hair follicle – Hairs are keratinized filaments that developed from an invagination of the epidermis called the hair follicle. They are present over almost the entire body, being absent from the sides and palmar surfaces of the hands, from the sides and plantar surfaces of the feet, from the lips, and from the region around the urogenital orifices.

Half Life – Is the time taken for the drug concentration to be reduced by one half.

Heart assist device – A mechanical device that is surgically implanted to ease the workload of the heart.

Heart attack – Death of, or damage to, part of the heart muscle due to an insufficient blood supply.

Heart block – A delay or interference of the conduction mechanism whereby impulses do not go through all or a major part of the myocardium.

Heartbeat – one complete contraction of the heart.

Heartburn – a burning feeling in the chest or area just above the stomach, caused by acid moving up the esophagus from the stomach.

Heat cramps – Painful and often incapacitating cramps in muscles. Heat cramps are caused by depletion of salt in the body as a result of heavy sweating, and ingestion of water without replacing salt.

Heat exchanger – used to alter temperature of blood by principle of conduction; may be free-standing or, more commonly, incorporated into oxygenator system.

Heat exhaustion – Weakness, lassitude, dizziness, visual disturbance, feeling of intense thirst and heat, nausea, vomiting, palpitations, tingling and numbness of extremities after exposure to a hot environment.

Heat hyper pyrexia – Rise in body temperature with moist skin and mental dysfunction, caused by exposure to an extremely hot environment.

Heat strain – Physiological and behavioral responses of the body as a result of heat exposure.

Heat stroke – Acute illness caused by overexposure to heat. Symptoms are dry, hot skin, high body temperature (usually over 105F) and mental dysfunction.

Heat Transfer – Heat Transfer, in physics, process by which energy in the form of heat is exchanged between bodies or parts of the same body at different temperatures.

Helicobacter pylori (H. pylori) – Bacteria found in the stomach that can damage the lining of the stomach and upper small intestine, leading to ulcer formation.

Hematocrit – Refers to the amount of blood that is occupied by red blood cells.

Hematomas – they results when small blood vessels are broken by the injury.

Hematuria – the presence of red blood cells (RBCs) in the urine.

Hemodilution – an increase in the volume of blood plasma resulting in reduced concentration of red blood cells.

Hemodynamics – Explains how the dimensions and configuration of the vasculature, combined with the fluidity of the blood, determine the way blood is distributed to and within organs.

Hemoglobin – brightens in color when saturated with oxygen (oxyhemoglobin) and darkens when oxygen is removed (deoxyhemogloblin).

Hemolysis – Damage to blood cells

Hemolytic uremic syndrome – a rare kidney disorder that mostly affects children under the age of 10. It is often characterized by: damage to the lining of blood vessel

Hemostasis – cessation of bleeding. Arrest of bleeding or of circulation. When equilibrium within the body is maintained, homeostasis is said to occur. The human body maintains a steady internal environment for the proper functioning of the body. Maintaining a constant internal environment requires the body to make many adjustments. Adjustments within the body are referred to as regulation of homeostasis. Homeostatic regulation is comprised of three parts: a receptor, a control center and an effector. The receptor functions by receiving information about any changes that are occurring in the environment while the control center processes that information and the effector executes the commands of the control center by making changes in response. All human body systems work together to maintain homeostasis.

Hemotrophic nutrition is a term used to describe in late placenta development the transfer of blood-borne nutrition from maternal to embryo/fetus compared to early histiotrophic nutrition.

Heparin – An acid occurring in tissues, mostly in the liver. It can be produced chemically and can make the blood incoaguable if injected into the blood stream intravenously.

Hepatic – Pertaining to the liver.

Hepatitis – inflammation of the liver that sometimes causes permanent damage; caused by viruses, drugs, alcohol, or parasites. Hepatitis has the following forms:

Hepatitis A – a form of infectious hepatitis caused by the hepatitis A virus. The virus may be spread by fecal-oral contact, fecal-infected food or water, and may also be spread by a blood-borne infection (which is rare).

Hepatitis B – a form of infectious hepatitis caused by the hepatitis B virus. Transmission of the hepatitis B virus occurs through blood and body fluid exposure such as blood, semen, vaginal secretions, or saliva.

Hepatitis C – a form of infectious hepatitis caused by the hepatitis C virus. Transmission of the hepatitis C virus occurs primarily from contact with infected blood, but can also occur from sexual contact or from an infected mother to her baby.

Hepatitis D – a form of infectious hepatitis caused by the hepatitis (Delta) virus. This form of hepatitis can only occur in the presence of hepatitis B. Transmission of hepatitis D occurs the same way as hepatitis B.

Hepatitis E – a form of infectious hepatitis caused by the hepatitis E virus. This form of hepatitis is similar to hepatitis A. Transmission occurs through fecal-oral contamination. Hepatitis E is most common in poorly developed countries and is rarely seen in the US.

Hepatitis G – the newest form of infectious hepatitis. Transmission is believed to occur through blood and is seen in IV drug users, individuals with clotting disorders, such as hemophilia, and individuals who require hemodialysis for renal failure.

Hernia – a section of intestine or other internal organ that pushes through an opening in an abdominal muscle.

Herniorrhaphy – an operation done to repair a hernia.

Hertz – A unit of frequency equal to one cycle per second.

Hetrotrophic – xenogeneic transplantation

High voltage current – Current in which the wave form has an amplitude of greater than 150 volts with a relatively short pulse duration of less than 100 sec.

Hirschsprung's disease – Caused by malformation of a baby's large intestine during pregnancy. Some of the nerve cells that are normally present are missing, causing problems moving stool through the intestine. This can cause obstruction (blockage) of the intestine.

Histiotrophic nutrition is a term used to describe in early placenta development the initial transfer of nutrition from maternal to embryo (histiotrophic nutrition) compared to later blood-borne nutrition (hemotrophic nutrition). Histotroph is the nutritional material accumulated in spaces between the maternal and fetal tissues, derived from the maternal endometrium and the uterine glands. This nutritional material is absorbed by phagocytosis initially by blastocyst trophectoderm and then by trophoblast of the placenta. In later placental development, nutrition is by the exchange of blood-borne materials between the maternal and fetal circulations, hemotrophic nutrition.

Hofbauer cells are found within placental villi connective tissue. These play a role as macrophages of mesenchymal origin with potentially additional functions (remodeling, vasculogenesis, and regulation of stromal water content).

Hormone – An organic chemical messenger that is produced in one part of the body and transported to another part where it signals cells to alter some aspect of metabolism.

Hydatiform mole is a uterine tumor with "grape-like" placenta appearance without enclosed embryo formation, arises mainly from a haploid sperm fertilizing an egg without a female pronucleus. It is one form of gestational trophoblastic disease (GTD), a number of abnormalities including hydatiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT).

Hydrocephalus – abnormal accumulation of body fluids within the skull.

Hydrochloric acid – acid made by the stomach that breaks down proteins in the foods we eat.

Hydrocollator – A synthetic hot (1700 F) or cold (00 F) gel used as an adjunctive modality to stimulate tissue temperature rise or tissue temperature lowering.

Hydrocortisone – An antinflamatory steroid.

Hydrogen breath test – a test that measures the amount of hydrogen in the breath, and helps diagnose lactose intolerance. If the body is unable to digest lactose properly, it will make excess amounts of hydrogen.

Hydrogymnastics – Exercises using the buoyant properties of immersion in water.

Hydronephrosis – a condition that occurs as a result of urine accumulation in the upper urinary tract. This usually occurs from a blockage somewhere along the urinary tract.

Hydrostatic pressure- The pressure exerted by a liquid at rest.

Hydrotherapy – Cryotherapy and thermotherapy techniques that use water as the medium for heat transfer.

Hyperactive – describes a situation in which a body tissue is especially likely to have an exaggerated reaction to a particular situation.

Hyperbilirubinemia – too much bilirubin in the bloodstream, due to liver problems. Causes a yellow color of the skin known as jaundice.

Hyperkalemia – Plasma K levels above 8mEq/L.

Hyperstimulation analgesia – See stimulus-produced analgesia.

Hypertension – The elevated blood pressure develops when the body's blood vessels narrow, causing the heart to pump harder than normal to push blood through the narrowed openings.

Hyperthermia – Exceptionally high fever especially when induced artificially for therapeutic purposes.

Hyperventilation – excessive rate and depth of respiration leading to abnormal loss of carbon dioxide from the blood.

Hypodermis – Layer of connective tissue, looser than that of the dermis. It contains a variable amount of adipose tissue.

Hypotension – abnormally low blood pressure.

Hypothalamus – Part of the brain that regulates the pituitary gland, the autonomic system, emotional responses, body temperature, water balance, and appetite; located below the thalamus.

Hypothermia – having a body temperature below normal. A technique of lowering body temperature, usually between 78˚ and 90˚ F. (26˚ and 32.5˚ C.), to reduce oxygen need during surgery and in hypoxia, to reduce blood pressure.

Hypothermia – an increase in body temperature.

Ileum – the lower end of the small intestine.

Impedance – Resistance of the tissue to the passage of electrical current.

In vivo – Occurring in a living organism.

Indifferent or dispersive electrode – Large electrode used to spread out electrical charge.

Indigestion – feeling of nausea, bloating, gas, and/or heartburn caused by poor digestion.

Induction electrodes – Electrical current is passed through a coil that in turn gives off eddy currents of electromagnetic energy. This energy is absorbed by the tissues and heating occurs as a result of the resistance of the tissues.

Inferior vena cava – The large vein returning blood from the legs and abdomen to the heart.

Inflammatory arthritis – Inflammatory types of arthritis are characterized by their tendency to cause inflammation in joints and tendons.

Inflammatory bowel disease (IBD) – diseases that cause irritation and ulcers in the intestinal tract. Crohn's disease and ulcerative colitis are the most common inflammatory bowel diseases.

Infrared – The portion of the electromagnetic spectrum associated with thermal changes; located adjacent to the red portion of the visible light spectrum. That part of the electromagnetic spectrum dealing with infrared wavelengths.

Inguinal hernia – part of the small intestine that pushes through an opening in the abdominal muscle, causing a bulge underneath the skin in the groin area.

Insensible fluid loss is a loss that cannot be easily measured. Some sources say insensible losses account for 500 to 650 ml/day (0.5 to 0.6 qt.) of water in adults. This loss includes fluid lost through perspiration and as water vapor in expired air. Some sources say insensible losses account for 500 to 650 ml/day (0.5 to 0.6 qt.) of water in adults.

Inspiration – inhaling; taking in oxygen.

Inspiratory capacity – The maximal volume of gas that can be inspired from the resting expiratory level.

Inspiratory Reserve Volume – Volume that can be inhaled during forced breathing in addition to tidal volume—3000mL

Inspiratory reserve volume – Maximal volume of gas that can be inspired from the end-inspiratory position.

Integumentary system – It performs a number of functions related to its location on the surface of the body. It prevents protection against physical, chemical, and biological injury, it prevents water loss, it serves as a large receptor for a general sensation (pain, pressure, touch, temperature). It also functions in heat regulation and it excretes certain substances through the sweat glands.

Interstitial cystitis – a complex, chronic disorder characterized by an inflamed or irritated bladder wall.

Interstitial trophoblast – invades the decidual stroma.

Intestinal flora – the normal bacteria, yeast, and fungi found in the intestines that aid in digestion.

Intestinal mucosa – the lining of the intestines, through which nutrients and water are absorbed into the body.

Intestine – digestive organs found in the abdomen, also known as either the large or small bowel. The small intestine removes nutrients from food to be used for energy, while the large intestine absorbs water from the digested food and processes it into stool. Intestine absorbs nutrients from the foods we eat.

Intolerance – allergy to a food or other substance.

Intracardiac vent – a device used to decompress cardiac chambers and to aspirate air and blood that is returned to cardiotomy reservoir.

Intracellular fluid – The cytosol.

Intracranial pressure – will cause internal or external herniation.

Intrathoracic – Within the thoracic cavities

Intravenous pyelogram (IVP) – a series of x-rays of the kidney, ureters, and bladder with the injection of a contrast dye into the vein to detect tumors, abnormalities, kidney stones, or any obstructions, and to assess renal blood flow.

Intussusception – a disorder in which the intestine folds into itself in a telescope fashion, causing obstruction (blockage).

Iris – The pigmented portion of the eye.

Islets of Langerhans – Also called Islands of Langerhans, irregularly shaped patches of endocrine tissue located within the pancreas of most vertebrates. They are named for the German physician Paul Langerhans, who first described them in 1869. The normal human pancreas contains about 1,000,000 islets.

Iuxtaglomerular apparatus – A structure in the kidney that secretes rennin in response to a decrease in blood pressure.

Jaundice – a yellow color of the skin and eyes that is caused by too much bilirubin in the bloodstream due to liver problems.

Jejunum – the middle section of the small intestine.

Keratin – A horny, water-insoluble protein that is a constituent of intermediate filaments in animal cells and is found in the epidermis of vertebrates: in nails, feathers, hair, horns, scales and claws.

Kidney – either of two bean-shaped excretory organs that filter wastes (especially urea) from the blood and excrete them and water in urine; urine passes out of the kidney through ureters to the bladder

Kidney stone – a solid piece of material that forms from crystallization of excreted substances in the urine.

Kidney transplantation – a procedure that places a healthy kidney from one person into a recipient's body.

Lacerations – it is the tearing of frontal and temporal lobes or blood vessels caused by brain rotating across ridges inside skull.

Lactase – an enzyme in the small intestine needed to digest lactose, a sugar found in milk and milk products.

Lactase deficiency – lack of an enzyme made by the small intestine called lactase, which prevents the body from digesting lactose (a sugar found in milk and milk products) properly.

Lactose tolerance test – a test that checks the body's ability to digest lactose (a sugar found in milk and milk products). The child drinks a liquid with lactose in it, and then the amount of lactose in the bloodstream is measured with a blood sample.

Lamina propria – A highly vascular layer of connective tissue under the basement membrane lining a layer of epithelium.

Laparoscope – a tube with a camera lens attached that looks inside organs to check for abnormalities. Often used in surgery to look inside the body and avoid making large incisions.

Laparoscopy – a procedure that uses a tube with a light and a camera lens at the end (laparoscope) to examine organs, check for abnormalities, or perform minimally invasive surgeries. Laparoscopy is a surgery, which avoids making large incisions. Tissue samples may also be taken for examination and testing.

Large intestine (Also called the colon) – The last section of the digestive tract, from the cecum to the rectum; absorbs water from digested food and processes it into stool.

Larynx – The organ at the upper end of the trachea that contains the vocal cords.

Limbic system – is the region of the brain that wraps around the brain stem and lies beneath the cerebrum.

Lipid – A fatty substance insoluble in blood.

Liver – a digestive organ located on the right side of the abdomen, under the ribs. Has many important functions, including storing and helping make blood, making bile (which aids in the digestion of fats in the food we eat), processing medicines and removing toxins from the bloodstream, and changing food and fats stored in our bodies into energy.

Liver function tests – blood tests that indicate how well the liver is working.

Lobectomy – removal of an entire lobe of the lung.

Lower esophageal sphincter – a muscle at the top portion of the stomach relaxes to allow food to pass from the esophagus to the stomach when we eat, and closes to keep food from moving back into the esophagus from the stomach.

Lower GI series – a study that looks at the rectum, the large intestine, and the lower part of the small intestine. A fluid called barium that shows up well on x-rays is given into the rectum as

an enema. X-rays of the abdomen shows strictures (narrowed areas), obstructions (blockages), and other problems.

Low-voltage current – Current in which the waveform has an amplitude of less than 150 volts.

Lumen – The cavity of a tubular organ or instrument.

Lung – An internal respiratory organ that functions in gas exchange; enables a person to breathe air.

Lung capacity – The amount of gas contained n the lung at the end of maximal inspiration.

Lung volume – the amount of air the lungs hold.

Lymph – The fluid content of the lymphatic vessels, similar in composition to the interstitial fluid.

Lymphatic system: Network of lymphatic vessels that play a central role in the body's defense system.

Magnetic field – A technique of heating the tissues in shortwave diathermy in which the patient is not part of the electrical circuit.

Magnetic resonance imaging (MRI) – a diagnostic procedure that uses a combination of large magnets, radiofrequencies, and a computer to produce detailed images of organs and structures within the body.

Malabsorption syndrome – problems with how the small

Malignant tumors – malignant tumors of the brain are more common that benign ones; the most frequent of all are the liomas, which arise form the neuroglial cells.

Malnutrition – a situation caused by eating a poorly balanced diet, or by not eating enough food to meet the body's needs.

Mass transfer – It is when a system contains two or more components whose concentrations vary from point to point, there is a natural tendency for mass to be transferred, minimizing the concentration differences within the system and moving it towards a equilibrium. It is the transport of one component from a region of higher concentration to that of a lower concentration.

Massive chronic intervillositis (MCI) **–** Maternal blood-filled space is filled with CD68-positive histiocytes and an increase in fibrin, occurring more commonly in the first trimester.

Maximal voluntary ventilation: The volume of air that a subject can breathes with maximal effort over a given time interval.

Mean blood pressure – average blood pressure, taking account of the rise and fall that occurs with each heartbeat. It is often estimated by multiplying the diastolic pressure by two, adding the systolic pressure, and then dividing this sum by three.

Mechanical effects – Ultrasonic effects that involve movement as a result of vibratory motion.

Mechanical valves – Artificial valves made from metal, plastic, and/or pyrolytic carbon. They have excellent durability and most will last indefinitely.

Meckel's diverticulum – A problem that occurs as a baby is developing during pregnancy, in which a small pouch (or sac) forms

Meconium myonecrosis is a prolonged meconium exposure leads to toxic death of myocytes of placental vessels (umbilical cord or chorionic plate).

Membrane oxygenator – uses a semipermeable membrane through which oxygen diffuses into, and carbon dioxide diffuses out of, desaturated blood; no direct blood-gas interface exists, preferred method for long bypass runs.

Membrane – A thin layer of tissue that covers a surface or divides a space or organ.

Meninges – The three membranes that envelop the brain and spinal cord: the dura madre, arachnoid, and pia madre.

Meningitis – infection of the cerebrospinal fluid.

Metabolic Acidosis – Plasma K levels below 2 mEq/L. A type of acidosis caused by the inability to excrete hydrogen ions, the production of numerous fixed and/or organic acids, or a severe bicarbonate loss [all by H2].

Metabolic rate – Rate of energy (heat) production of the body which varies with the level of activity.

Microshock – An electrical shock that is imperceptible because of a leakage of current of less than 1 mamp.

Micturition – Urination.

Mitral valve – The structure that controls blood flow between the heart's left atrium (upper chamber) and left ventricle (lower chamber).

Modulation – Refers to any alteration in the magnitude or any variation in the duration of an electrical current.

Molecule – The smallest unit of matter of a substance that retains all the physical and chemical properties of that substance, consisting of a single atom or a group of atoms bonded together; e.g., Ne, H_2, H_2O.

Morbidity – state of being diseased. The number of sick persons or cases of disease in relationship to a specific population.

Motility – the movement of food through the digestive tract, aided by contractions of muscles in the stomach and intestines known as peristalsis.

Mucus – a thick, jelly-like substance made by the intestines and other organs of the body (such as the nose), that helps coat and protect the lining of the organ. Mucus also helps stool pass through the large intestine and rectum more easily.

Myelin sheath – The white fatty material that forms a sheath around the axons of certain nerve cells, which are then called myelinated nerve fibers.

Myoepithelial cells – They move secretions out of the gland by contraction.

Nanoparticle sensors – tiny particles on the order of a single atom that will recognize compounds.

Nausea – a feeling of needing to vomit (throw-up).

Necrosis – when tissue in an organ dies due to lack of blood supply.

Necrotizing enterocolitis – a situation that may affect underweight or premature infants, and occurs when part of the intestine is damaged or destroyed by a bacterial infection.

Nephrectomy – surgery to remove the kidney; the most common treatment for kidney cancer.

Nephritis – inflammation of the kidneys.

Nephrolithotomy – a small cut is made in the patient's back and a narrow tunnel is made through the skin to the stone inside the kidney. The physician can remove the stone through this tunnel.

Nephrology – the medical specialty concerned with diseases of the kidneys.

Nephron – The functional, microscopic unit of the kidney.

Nephrotic syndrome – a condition characterized by high levels of protein in the urine, low levels of protein in the blood, tissue swelling, and high cholesterol.

Nerve – A bundle of axons or dendrites wrapped in connective tissue that conveys impulses between the central nervous system and some other part of the body.

Nervous System – System of specialized cells (neurons, or nerve cells) that conduct stimuli from a sensory receptor through a neuron network to the site (e.g., a gland or muscle) where the response occurs.

Nervous tissue – a type of tissue specialized for conducting electrochemical impulses.

Neuroblastoma is a fetal malignancy that leads to an enlarged placenta, with tumor cells in the fetal circulation and rarely in the chorionic villi.

Neurogenic bladder (Also called neuropathic bladder) – a bladder disorder that can be caused by a tumor or other condition of the nervous system.

Neuron – A nerve cell; a conducting cell of the nervous system that typically consists of a cell body, dendrites, and an axon.

Neurotransmission – transmission of information between neutrons.

Neurotransmitter – A chemical messenger used by neurons to transmit impulses across the synapse.

Nissen fundoplication – an operation that helps treat gastroesophageal reflux disease (GERD). The fundus (top of the stomach) is pulled around the esophagus and sewn. This helps prevent food from moving back from the stomach into the esophagus by creating a muscular band at the top of the stomach, which becomes tighter as the stomach fills up.

Nitabuch's layer (fibrinoid layer) is formed at maternal/fetal interface during placentation and is thought to act to prevent excessively deep conceptus implantation.

Norepinephrine – A neurotransmitter that may enhance pain. When it is inhibited, analgesia is increased. Increased levels in the central nervous system decrease analgesia.

Nusselt number – is a dimensionless number which measures the enhancement of heat transfer from a surface which occurs in a 'real' situation, compared to the heat transfer that would be measured if only conduction could occur. Typically it is used to measure the enhancement of heat transfer when convection takes place.

Obstruction – a blockage in the digestive tract that prevents the forward movement of foods and liquids as they are digested.

Occipital lobes: Posterior areas of the cerebrum; interpret visual stimuli from the retina of the eye.

Occult blood – blood in the stool that is not visible to the naked eye.

Ohm's law – The current in an electrical circuit is directly proportional to the voltage and inversely proportional to the resistance.

Oligohydramnios – Condition that occurs in pregnant women when the amniotic fluid is < 5 cm.

Opening Pressure – To measure CSF opening pressure, the patient must be in the lateral decubitus position with the legs and neck in a neutral position.

Organ of Corti – The structure within the inner ear that contains receptor cells that sense sound vibrations.

Organ system – Body system; an organized group of tissues and organs that work together to perform a specialized set of functions.

Osmosis – This process differs primarily from ordinary diffusion in that only the solvent, rather than the solute, is able to penetrate the separating membrane. Usually, the solute molecules that cause the osmotic driving force are unable to pass through the membrane because of their size. In ordinary diffusion, all species are able to penetrate the membrane, although the permeability may be different for each species. Here, water moves through permeable membranes. Water moves from an area of high/low water potential to one of low/high water potential until a dynamic equilibrium is reached.

Osmotic pressure – The pressure for movement of a solvent across a membrane that is permeable to that solvent.

Osteoarthritis – The most common form of arthritis is osteoarthritis (OA), also known as degenerative joint disease. OA affects about 28 million Americans, 80 percent of whom are women. The disease is most prevalent in people aged 55 and older.

Ostomy – an operation that is done when there is damage to a section of intestine. It creates an opening in the wall of the abdomen, and brings a portion of intestine through the opening so stool can leave the body.

Otoliths – Small calcium carbonate crystals in the saccule and utricule of the inner ear; sense gravity and are important in static equilibrium.

Overflow incontinence – leakage of urine that occurs when the quantity of urine produced exceeds the bladder's capacity to hold it.

Oxygen dissociation curve – A curve depicting the percentage saturation of hemoglobin with oxygen, as a function of certain variables such as oxygen concentration, carbon dioxide concentration, or pH.

Oxygenation – saturation or combination with oxygen, as the aeration of the blood in the lungs.

Oxygenator – performs gas exchange functions; provides oxygen, removes carbon dioxide; contains an arterial reservoir.

Oxyhemoglobin – Hemoglobin that has combined with oxygen.

Pacemaker (of the heart) – See sinoatrial node.

Pad electrodes – Capacitor type electrode used with shortwave diathermy.

Palpitation – sensation of rapid heartbeats.

Pancreas – Large gland located in the abdominal cavity. The pancreas produces pancreatic juice containing digestive enzymes; also serves as an endocrine gland; secreting the hormone insulin and glucagons.

Papilla – A small nipple – like projection or elevation, such as the papilla at the base of each hair follicle.

Papillary layer- It consists of loose connective tissue. It is located immediately under the epidermis and is separated from it by the basal lamina. The papillary layer is a relatively thin layer extending into the dermal papillae and ridges. It contains blood vessels that serve, but do not enter, the epidermis.

Paraffin bath – A combined paraffin and mineral oil immersion technique in which the paraffin sub stance is heated to 126° F for conductive heat gains; commonly used on the hands and feet for distal temperature gains in blood flow and temperature.

Parathyroid gland – Small, pea-sized glands closely adjacent to the thyroid gland; their secretion regulates calcium and phosphate metabolism.

Parathyroid hormone – Hormone secreted by the parathyroid glands; regulates calcium and phosphate metabolism.

Parenteral nutrition – a means of providing protein, fats, carbohydrates, fluid, and vitamins to the body through a special solution given through a vein into the bloodstream.

Partial nephrectomy – surgery to remove the kidney; only the part of the kidney that contains the tumor is removed.

Pediatric gastroenterologist – a physician who treats infants and children with diseases of the digestive system.

Peptic – related to the stomach and the upper part of the small intestine (duodenum).

Peptic ulcer – a sore in the lining of the esophagus, stomach, or duodenum (beginning of the small intestine); often caused by a bacteria called Helicobacter pylori.

Percutaneous – effected through the skin. Applying a medicated ointment by friction, or removal or injection by needle.

Perforation – a hole in the wall of an organ.

Perfusion – passing of a fluid through spaces. Supplying an organ or tissue with nutrients and oxygen by injecting blood or a suitable fluid into an artery.

Peristalsis – wave-like movements of food forward through

Peritonitis – an infection inside the abdominal cavity.

Persistent right umbilical vein (PRUV) is a placental cord abnormality associated with fetal abnormalities and poor neonatal prognosis.

Pessary – a device placed in the vagina to hold the bladder in place or to treat a prolapsed uterus.

Peyronie's disease – A plaque, or hard lump, that forms on the erection tissue of the penis. The plaque often begins as an inflammation that may develop into a fibrous tissue.

pH – The negative exponent of the hydrogen ion concentration, expressed in moles per liter.

Pharynx – Part of the digestive tract. It is bounded anteriorly by the mouth and nasal cavities and posteriorly by the esophagus and larynx; the throat region.

Pinocytosis – The mechanical process that results in large molecules being engulfed in the cell membrane and subsequently transported to the interior is a primary process in supporting cell function. The driving forces for this process are not completely understood.

Placenta (Greek, *plakuos* = flat cake): The developmental organ formed from maternal and fetal contributions in animals with placental development. In human, the placenta at term is a discoid shape "flat cake" shape; 20 cm diameter, 3 cm thick and weighs 500-600 gm. Placenta are classified by the number of layers between maternal and fetal blood (Haemochorial, Endotheliochorial and Epitheliochorial) and shape (Discoid, Zonary, Cotyledenary and Diffuse). The placenta has many different functions including metabolism, transport and endocrine.

Placenta accrete – The abnormal placental adherence, either in whole or in part of the placenta with absence of decidua basalis, leading to retention as an after-birth to the underlying uterine

wall. The incidence of placenta accreta also significantly increases in women with previous cesarean section compared to those without a prior surgical delivery.

Placenta increta occurs when the placenta attaches deep into the uterine wall and penetrates into the uterine muscle, but does not penetrate the uterine serosa. Placenta increta accounts for approximately 15–17% of all cases.

Placenta percreta: Placental villi penetrate myometrium and through to uterine serosa.

Placenta previa – This condition occurs in approximately 1 in 200 to 250 pregnancies. In the third trimester and at term, abnormal bleeding can require caesarian delivery and can also lead to "Abruptio Placenta". Ultrasound screening programs during 1st and early 2nd trimester pregnancies now include placental localization. Diagnosis can also be made by transvaginal ultrasound.

Placental arteries (umbilical arteries) **–** In placental animals, the blood vessels which develop within the placental cord carrying relatively deoxygenated blood from the embryo/fetus to the placenta. In humans, there are two placental arteries continuous with the paired internal iliac arteries (hypogastric arteries) arising off the dorsal aortas. At birth this vessel regresses and form the remnant medial umbilical ligament.

Placental cord (umbilical cord) **–** The placental cord is the structure connecting the embryo/fetus to the placenta. It is initially extra-embryonic mesoderm forming the connecting stalk within which the placental blood vessels (arteries and veins) form. In human placental cords the placental blood vessels are initially paired, later in development only a single placental vein remains with a pair of placental arteries. This structure also contains the allantois, an extension from the hindgut cloaca then urogenital sinus. Blood collected from the placental cord following delivery is a source of cord blood stem cells.)

Placental diameter is measured in the transverse section by calculating the maximum dimensions of the chorionic surface.

Placental growth factor (PlGF) **–** A growth factor of the vascular endothelial growth factor (VEGF) family, released from the placental trophoblast cells and other sources that stimulates blood vessel growth.

Placental malaria is a malarial infection of the placenta by sequestration of the infected red blood cells. This condition can be common in regions where malaria is endemic with women carrying their first pregnancy.

Placental membranes (chorionic membrane; amniotic membrane) are general terms to describe the membrane bound extra-embryonic fluid-filled cavities surrounding the embryo then fetus. In humans, the amniotic membrane and chorionic membrane fuse.

Placental thickness is measured at its mid-portion from the chorionic plate to the basilar plate, on a longitudinal plane (less than 4 cm at term). It excludes any abnormalities (fibroids, myometrial contractions, or venous lakes).

Placental vein (umbilical vein): In placental animals, the blood vessels which develop within the placental cord carrying relatively oxygenated blood from the placenta to the embryo/fetus. In humans, there are initially two placental veins which fuse to form a single vein. The presence of paired veins in the placental cord can be indicative of developmental abnormalities.

Placental volume is measured by a range of different methods and calculations, more recently with three-dimensional ultrasound.

Placentophagia is a term used to describe the maternal ingestion of after birth materials (placental membranes and amniotic fluid) that can occur following mammalian parturition (birth).

Plasma clearance – the sum of all the drug elimination processes of the body.

Plasma – The fluid ground substance of whole blood; what remains after the cells have been removed from a sample of whole blood.

Platelets – Small packets of cytoplasm that contain enzymes important in the clotting response; manufactured in bone marrow by megakaryocytes.

Plethysmography – The recording of the changes in the volume of a body part as modified by the circulation of the blood in it.

Pleura – membrane that covers the outside of the lung.

Plicae Circulares – Plicae circulares are macroscopically visible, crescent-shaped folds of the mucosa and submucosa. Plicae circulares extend around one-half to two-thirds of the circumference of the lumen of the small intestine.

Pneumonectomy – removal of an entire lung.

Polycystic kidney disease (PKD) – a genetic disorder characterized by the growth of numerous cysts filled with fluid in the kidneys.

Polyhydramnios – Condition that occurs in pregnant women when the amniotic fluid is > 25 cm.

Polymeric degradation (biodegradation) – In this case, as with the diffusion method, the drug is contained within a polymer membrane or matrix. The polymer is designed to degrade and release the drug at a specific location in the body.

Portal hypertension – high blood pressure in the portal vein that carries blood to the liver.

Portal vein – the large vein that carries blood to the liver from the spleen and intestines.

Pouch – a specialized collection bag worn over an ostomy to collect stool.

Preeclampsia – Abnormal state of pregnancy characterized by hypertension and fluid retention and albuminuria; Can lead to eclampsia if untreated.

Premature ejaculation (PE) – the inability to maintain an erection long enough for mutual satisfaction.

Priapism – inflammation of the penis.

Prolapse – when part of the body (for instance, a section of intestine) slips from its normal position.

Prostatalgia – pain in the prostate gland.

Prostate – a sex gland in men. It is about the size of a walnut, and surrounds the neck of the bladder and urethra, the tube that carries urine from the bladder. It is partly muscular and partly glandular, with ducts opening into the prostatic portion of the urethra. It is made up of three lobes: a center lobe with one lobe on each side.

Prostatectomy – surgical procedure for the partial or complete removal of the prostate.

Prostate-specific antigen (PSA) blood test – a blood test used to help detect prostate cancer by measuring a substance called prostate-specific antigen produced by the prostate.

Prostatism – any condition of the prostate that causes interference with the flow of urine from the bladder.

Prostatitis – an inflamed condition of the prostate gland that may be accompanied by discomfort, pain, frequent urination, infrequent urination, and, sometimes, fever.

Protein – one of three main types of foods, along with fats and carbohydrates. Proteins are digested into smaller pieces called amino acids that are used by the body to build and repair cells. Proteins are found in meats, eggs, milk products, and beans.

Proteinuria – large amounts of protein in the urine.

Proton pump inhibitors – medicines that affect how acid is produced by the stomach's "proton pump" system, thereby decreasing stomach acid.

Pulmonary – Referring to the lungs and respiratory system

Pulmonary artery – blood vessel delivering oxygen-poor blood from the right ventricle to the lungs.

Pulmonary autograft valves – A new approach for replacement of a diseased aortic valve involves moving the patients own pulmonary valve (the valve on the right side of the heart that leads to the pulmonary artery and the lungs just as the aortic valve leads to the aorta and the body) into the aortic position to replace a stenotic or regurgitant aortic valve.

Pulmonary circulation: The part of the circulation system that delivers blood to and from the lungs for oxygenation.

Pulmonary hypertension – abnormally high blood pressure in the arteries of the lungs.

Pulmonary minute volume (pulmonary ventilation): Volume of air respired per minute= tidal volume* breathes/min.

Pulmonary valve – The heart valve between the right ventricle and the pulmonary artery. It controls blood flow from the heart into the lungs.

Pulmonary vein – The blood vessels that carry newly oxygenated blood from the lungs back to the left atrium of the heart.

Pulsatile – pulsating; characterized by a rhythmic beat.

Pulsed ultrasound- Method of administering ultra-

Pump – apparatus that transfers fluids or gases by pressure. To force air or fluid into a cavity, as heart pumps blood.

Pyloric sphincter – the muscle between the stomach and the small intestine.

Pyloric stenosis – an enlargement of the muscle between the stomach and the small intestine, blocking the passage of food and liquids forward into the intestines.

Pyloroplasty – an operation that enlarges the opening between the stomach and small intestine so food and liquid can move forward and be digested normally.

Pylorus – where the stomach connects to the small intestine.

Radiograph- Record produced on a photographic plate, film, or paper by the action of roentgen rays or radium; specifically x-rays.

Rectal manometry – a test that measures the movements and strength of the rectal and anal sphincter muscles.

Rectum – lower end of the large intestine, leading to the anus.

Reference daily intake or **Recommended daily intake** (**RDI**) is the daily intake level of a nutrient that is considered to be sufficient to meet the requirements of 97–98% of healthy individuals in every demographic in the United States.

Reflux – digestive juices, food, and liquids moving backward from the stomach into the esophagus, and possibly into the mouth.

Reflux esophagitis – irritation of the lining of the esophagus due to movement of digestive juices backward from the stomach into the esophagus.

Regurgitation – When a valve leaks it is said to be regurgitant or to exhibit regurgitation

Relative humidity – The ratio of the water vapor content of air to the maximum possible water vapor content of air at the same temperature and air pressure

Renal angiography (Also called renal arteriography) – a series of x-rays of the renal blood vessels with the injection of a contrast dye into a catheter, which is placed into the blood vessels of the kidney; to detect any signs of blockage or abnormalities affecting the blood supply to the kidneys.

Renal blood flow (**RBF**) is the volume of blood delivered to the kidneys per unit time. In humans, the kidneys together receive roughly 22% of cardiac output, amounting to 1.1 L/min in a 70-kg adult male. RBF is closely related to **renal plasma flow** (**RPF**).

Renal plasma flow is the volume of plasma that reaches the kidneys per unit time. Renal plasma flow is given by the Fick principle.

Renal ultrasound – a non-invasive test in which a transducer is passed over the kidney producing sound waves, which bounce off of the kidney, transmitting a picture of the organ on a video screen. The test is used to determine the size and shape of the kidney, and to detect a mass, kidney stone, cyst, or other obstruction or abnormalities.

Repolarize – To return to a polarized state after a de-polarizing event.

Residual volume -Volume that remains in the lungs at all times **–** 1200 mL

Respiration – gas exchange from air to the blood and from the blood to the body cells.

Retina – The innermost of the three layers of the eyeball, which is continuous with the optic nerve and contains the light- sensitive rod and cone cells.

Reynolds number – is the most important dimensionless number in fluid dynamics providing a criterion for dynamic similarity. It is named after Osbourne Reynolds (1842–1912). The Reynolds number is used for determing whether a flow is laminar or turbulent. Laminar flow within e.g., pipes will occur when the Reynolds number is below the critical Reynolds number of

$Re_{crit,\ pipe} = 2300$ (or practically $Re > 3000$) and turbulent flow when it is above 2300 where the Reynolds number is based on the pipe diameter and the mean velocity v_s within the pipe. The value of 2300 has been determined experimentally and a certain range around this value is considered the transition region between laminar and turbulent flow.

Rh disease – A blood group antigen possessed by Rh-positive people; if an Rh-negative person receives a blood transfusion from an Rh-positive person it can result in hemolysis and anemia.

Richardson number – is named after Lewis Fry Richardson (1881–1953). It is the dimensionless number that expresses the ratio of potential to kinetic energy If the Richardson number is much less than unity, buoyancy is unimportant in the flow. If it is much greater than unity, buoyancy is dominant (in the sense that there is insufficient kinetic energy to homogenize the fluids). If the Richardson number is of order unity, then the flow is likely to be buoyancy-driven: the energy of the flow derives from the potential energy in the system originally.

Ritual purification is a feature of many religions. The aim of these rituals is to remove specifically defined uncleanliness prior to a particular type of activity, and especially prior to the worship of a deity. This ritual uncleanliness is not identical with ordinary physical impurity, such as dirt stains; nevertheless, body fluids are generally considered ritually unclean. Most of these rituals existed long before the germ theory of disease, and Figure prominently from the

earliest known religious systems of the Ancient Near East. Some writers remark that similarities between cleansing actions, engaged in by obsessive compulsive disorder sufferers and those of religious purification rites, point to an ultimate origin of the rituals in the personal grooming behavior of the primates, but others connect the rituals to primitive taboos. Some have seen benefits of these practices that as a point of health and preventing infections especially in areas where humans come in close contact with each other. While these practices came before the idea of the germ theory was public in areas that use daily cleaning, the destruction of infectious agents seems to be dramatic.

Rod – light sensitive cells of the retina that are particularly sensitive to dim light and mediate white and black vision.

Roller pump – uses positive displacement with rotating roller head to propel fluid; amount of flow is dependent on degree that tubing is occluded and on number of revoluions per minute; additional roller heads are used for cardiotomy suctions and venting.

Rossby number – named for Carl-Gustav Arvid Rossby, is a dimensionless number used in describing geophysical phenomena in the oceans and atmosphere. It characterises the ratio of inertial forces in a fluid to the fictitious forces arising from planetary rotation. It is also known as the *Kibel number.*

Rotavirus – a virus that causes diarrhea. It is the most common cause of infectious diarrhea in the United States, especially in children under 2 years old.

Rouleaux formation – agglomeration of RBC in the centerline of flow field

RVAD – Right Ventricular Assist Device: support system for the right ventricle of the heart.

Saliva – a fluid made by glands in the mouth that helps moisten and soften foods we chew, and begins the digestive process.

Salmonella – bacteria that can cause diarrhea, often found in uncooked eggs.

Scrotum --- The external sac of skin in males that contains the testes and their accessory organs.

Sebaceous gland – These glands develop as an outgrowth of the external root sheath of the hair follicle, usually several glands to one follicle. They secrete an oily substance called sebum.

Secondary vasodilatation – Dilation following exposure to cold to sustain viable tissues.

Semen – Fluid composed of sperm suspended in various glandular secretions that is ejaculated from the penis during orgasm.

Semilunar valves – Valves between the ventricles of the heart and the arteries that carry blood away from the heart; aortic and pulmonary valves.

Seminal vesicles – Glandular sacs that secrete a component of seminal fluid.

Shawnn cell – Supporting cells found in nervous tissue outside the central nervous system.

Sigmoid colon – the lower part of the large intestine that empties into the rectum.

Sigmoidoscopy – a test that uses a thin, flexible tube with a camera lens at the end to look at the inside of the rectum and lower large intestine for abnormalities.

Sinoatrial node: Mass of specialized cardiac muscle in which the impulse triggering the heartbeat originates; the peacemaker of the heart.

Skin (integument, cutis) – It forms the external covering of the body. The skin and its derivatives constitute the integumentary system. It consists of two main layers: The epidermis and the dermis.

Skull Fracture – it is braking of the bony skull caused by an accident.

Small intestine – the section of the digestive tract between the stomach and the large intestine. Most of digestion occurs here as nutrients are absorbed from food.

Small intestine – Portion of the digestive tract that extends from the stomach to the large intestine.

Smooth muscle – muscle that performs automatic tasks, such as constricting blood vessels.

Sodium – A mineral essential to life found in nearly all plant and animal tissue. Table salt (sodium chloride) is nearly half sodium.

Solvent drag, also known as **bulk transport**, is a phenomenon primarily in renal physiology, but it also occurs in gastrointestinal physiology. It is when solutes in the ultra-filtrate are transported back from the renal tubule by the flow of water rather than specifically by ion pumps or other membrane transport proteins. It generally occurs in the paracellular, rather than transcellular, pathway across the tubular cells. It is seen e.g., in the passive transport in renal sodium reabsorption, renal chloride reabsorption as well as renal urea handling.

Solvent-activated system – It employs a semi-permeable membrane (reservoir) containing a small, laser-drilled hole(s). Within the membrane there is a high concentration of an osmotic agent, either the drug itself or a salt, which causes water to enter through the membrane. The drug is then forced out through the hole because of the increased pressure. Drug release proceeds at a constant rate in solvent-activated systems.

Spallation – the release of micro-particles of plastic from the inner walls of tubing due to compression by roller-pumps.

Spasm – movement of a muscle that causes cramping and pain.

Specific heat – The amount of heat, measured in calories, required to raise the temperature of one gram of a substance by one Celsius degree.

Sperm disorders – problems with the production and maturation of sperm; the single most common cause of male infertility. Sperm may be immature, abnormally shaped, unable to move properly, or, normal sperm may be produced in abnormally low numbers (oligospermia).

Sphincter – a circular muscle that opens and closes at an entrance to an organ. Examples include the lower esophageal sphincter and the anal sphincter.

Sphincter muscles – circular muscles that help keep urine from leaking by closing tightly like a rubber band around the opening of the bladder.

Sphygmomanometer – An instrument for measuring blood pressure, especially arterial blood pressure.

Spinal cord – In vertebrates, the body's major nerve tract. In humans it is about 18 in. (45 cm) long, running from the base of the

brain through the vertebral column.

Spinal nerves – The nerves that emerge from the spinal cord.

Spirogram – record of the amounts of air being moved in and out of the lungs.

Spirometer – An instrument for measuring the air entering and leaving the lungs.

Spleen – an organ found on the left side of the abdomen, next to the stomach. Makes white blood cells that help fight infection and filters and cleanses the blood. Plays a role in immunity.

Steatorrhea – loose, greasy bowel movements caused by an inability of the body to absorb fat.

Stenosis – The narrowing or constriction of an opening, such as a blood vessel or heart valve.

Sternotomy – the operation of cutting through the sternum.

Stoma – a surgically created opening in an organ, such as the stomach (gastrostomy) or intestine (colostomy).

Stomach – Muscular region of the digestive tract extending from the esophagus to the small intestine.

Stool – waste products that remain after food is digested, including fiber, bacteria, mucus, undigested foods, and cells from the inside of the intestine. Passed through the rectum as a bowel movement.

Stratum basale- It is adjacent to the basal lamina. It is also called the stratum germinativum because it contains move toward the surface to replace those that have sloughed off.

Stratum Corneum – Is the exposed layer of both thick skin and thin skin; it is made up of dead cells.

Stress incontinence – the most common type of incontinence that involves the leakage of urine during exercise, coughing, sneezing, laughing, lifting heavy objects, or other body movements that put pressure on the bladder.

Stress ulcer – an ulcer in the esophagus, stomach, or upper small intestine caused by excess acid produced as a result of surgery, major burns, head injury, or other trauma.

Stricture – abnormal narrowing of a part of an organ.

Strouhal number – is a quantity describing oscillating flow mechanisms. Often, it is given as Sr = f*D/V where Sr is the Strouhal number, f is the frequency of vortex shedding, D is the hydraulic diameter of the object in the fluid flow and V is the velocity of the fluid. The Strouhal number is a function of the Reynolds number Re and in the region 200<Re<200,000 it is assumed to be equal to 0.2.

Superior vena cava – Main vein feeding back to the heart from systemic circulation above the heart.

Syncitiotrophoblast – are multinucleate cells that cover placental villi. These are currently thought to form by the fusion of another trophoblast cell the cytotrophoblasts, within the trophoblast layer (shell) of the implanting conceptus. In early development, these cells mediate implantation of the conceptus into the uterine wall and secrete the hormone (human Chorionic Gonadotrophin, hCG) responsible for feedback maintenance of the corpus luteum (in maternal ovary) and therefore maintaining early pregnancy.

Syncope – fainting; temporary loss of consciousness.

Syringohydromyelia – also called syrinx that is a fluid collection in the spinal cord.

Systemic – relating to a process that affects the body generally; in this instance, the way in which blood is supplied through the aorta to all body organs except the lungs.

Systemic circulation – circulation of blood throughout the entire body

Systole – The contraction, or period of contraction, of the heart, especially that of the ventricles. It coincides with the interval between the first and second heart sound, during which blood is forced into the aorta and the pulmonary trunk.

Systolic pressure – the highest pressure to which blood pressure rises with the contraction of the ventricles.

Temperature – The degree of hotness or coldness of a body or environment. A measure of the average kinetic energy of the particles in a sample of matter, expressed in terms of units or degrees designated on a standard scale.

Testis – one of the pair of male gonads that produce semen; suspended in the scrotum by the spermatic cords.

Thermal conductivity – The quantity of heat that passes in unit time through unit area of a plate whose thickness is unity, when its opposite faces differ in temperature by one degree.

Thermal – Pertaining to heat.

Thermotherapy – The use of heat in the treatment of pathology or disease.

Thick skin- Hairless skin where the epidermis is much thicker.

Thin skin- Contains hair except in certain locations; the epidermis is thinner.

Thrombophilias (protein C or S deficiency, factor V Leiden, sickle cell disease, antiphospholipid antibody) can generate an increased fibrin/fibrinoid deposition in the maternal or intervillous space; this can trap and kill villi.

Thrombosis – A blood clot that forms inside the blood vessel or cavity of the heart.

Thrombus – a blood clot obstructing a blood vessel or a cavity of the heart.

Thyroid gland – An endocrine gland that lies anterior to the trachea and releases hormones that regulate the rate of metabolism.

Thyroid hormones – Hormones, including thyroxin, secreted by the thyroid gland; stimulate rate of metabolism.

Tidal volume – Volume of gas inspired or expired during each quiet respiration cycle.

Total Lung Capacity – Total volume of air that the lungs can hold. TLC = VC + RV.

Total parenteral nutrition – see parenteral nutrition.

Trachea – The main trunk of the system of tubes by which air passes to and from the lungs.

Tracheoesophageal fistula – caused by improper development of the baby's trachea (windpipe) and esophagus during pregnancy. The esophagus does not connect to the stomach, and there is also an abnormal connection between the esophagus and the trachea. food cannot pass through to the stomach, and may pass into the trachea and then into the lungs, causing breathing problems.

Transcutaneous electrical nerve stimulation (TENS) – a method of providing pain relief using electrical signals, which are sent to the nerve endings.

Transdermal Drug Delivery – Is the transport of drug through the skin.

Transducer – A device that changes energy from one type to another.

Transmission – To pass through some medium.

Transrectal ultrasound of the prostate – a test using sound wave echoes to create an image of an organ or gland to visually inspect for abnormal conditions like gland enlargement, nodules, penetration of tumor through capsule of the gland and/or invasion of seminal vesicles. It may also be used for guidance of needle biopsies of the prostate gland and guiding the nitrogen probes in cryosurgery.

Transurethral hyperthermia – an investigative procedure that uses heat, usually provided by microwaves, to shrink the prostate.

Transurethral incision of the prostate (TUIP) – a procedure that widens the urethra by making some small cuts in the bladder neck, where the urethra joins the bladder, and in the prostate gland itself.

Transurethral laser incision of the prostate (TULIP) – the use of laser through the urethra that melts the tissue.

Transurethral resection of the prostate (TURP) – a surgical procedure by which portions of the prostate gland are removed through the penis.

Transurethral surgery – surgery in which no external incision is needed. For prostate transurethral surgery, the surgeon reaches the prostate by inserting an instrument through the urethra. See below for different types of transurethral surgery.

Transverse colon – the part of the intestine that lies horizontally in the abdomen, running straight across the abdomen from right to left.

Tricuspid aortic valve – The normal aortic valve has three cusps or leaflets, and is therefore called tricuspid (as opposed to a bicuspid aortic valve)**.** The valve connects the right atrium to the right ventricle.

Trophoblast – The superficial layer of the blastocyst that will be involved in implantation, hormone production, and placenta

Tunica vaginalis – a thin pouch that holds the testes within the scrotum.

Ulcer – a sore in the lining of the digestive tract.

Ulcerative colitis – a disease that causes irritation and ulcers in the lining of the large intestine and rectum. Also known as Inflammatory Bowel Disease.

Ultrasound (Also called sonography) – a diagnostic imaging technique which uses high-frequency sound waves and a computer to create images of blood vessels, tissues, and organs. Ultrasounds are used to view internal organs as they function, and to assess blood flow through various vessels.

Ultrasound imaging – Technique in which high frequency sound waves are used to provide an image (sonogram) of an internal structure.

Ultraviolet – The portion of the electromagnetic spectrum associated with chemical changes, located adjacent to the violet portion of the visible light spectrum.

Units – are standards for measurement of physical quantities that need clear definitions to be useful. Reproducibility of experimental results is central to the scientific method. To facilitate this we need standards, and to get convenient measures of the standards we need a **system of units**. Scientific systems of units are a formalization of the concept of weights and measures, initially developed for commercial purposes.

UNOS – United Network for Organ Sharing

Upper GI series – a test that looks at the organs of the upper part of the digestive system: the esophagus, stomach, and duodenum (upper small intestine). A liquid that shows up well on x-rays called barium is swallowed. X-rays are then taken to evaluate the digestive organs.

Urea – the nitrogen part of urine produced from the breakdown of protein.

Urea breath test – a test that measures the amount of urease in the breath, which is an enzyme that the bacteria Helicobacter pylori makes. This helps diagnose H. pylori infection, which can help determine the cause for ulcers in the digestive tract.

Ureter – One of the paired tubular structures that conducts urine from the kidney to the bladder.

Ureterocele – the portion of the ureter closest to the bladder becomes enlarged because the ureter opening is very tiny and obstructs urine outflow; urine backs up in the ureter tube.

Ureteroscope – an optical device which is inserted into the urethra and passed up through the bladder to the ureter; to inspect the opening of the ureters.

Urethra – The tube that conducts urine from the bladder to the outside of the body.

Urethritis – infection limited to the urethra.

Urge incontinence – the inability to hold urine long enough to reach a restroom. It is often found in people who have conditions such as diabetes, stroke, dementia, Parkinson's disease, and multiple sclerosis, but may be an indication of other diseases or conditions that would also warrant medical attention.

Urinalysis – laboratory examination of urine for various cells and chemicals, such as red blood cells, white blood cells, infection, or excessive protein.

Urinary bladder – An organ that receives urine from the ureters and temporarily stores it.

Urinary incontinence – the loss of bladder control.

Urinary syste – Body system that consists of kidneys, urinary bladder, and associated ducts.

Urinary tract infection (UTI) – an infection that occurs in the urinary tract, often caused by bacteria such as Escherichia coli. A UTI often causes frequent urination, pain and burning when urinating, and blood in the urine.

Urine flow test – measures how quickly the urine is flowing. A reduced flow may suggest benign prostatic hyperplasia (BPH).

Urogenital – refers to the urinary and reproductive systems.

Urology – the branch of medicine concerned with the urinary tract in both genders, and with the genital tract or reproductive system in the male.

Uterine wall is a wall of the uterus.

Uterus (Also called the womb) is a hollow, pear-shaped organ located in a woman's lower abdomen, between the bladder and the rectum, that sheds its lining each month during menstruation and in which a fertilized egg (ovum) becomes implanted and the fetus develops.

Uterus – The hollow, muscular organ of the female reproductive tract in which the fetus undergoes development.

VACTERL – A syndrome involving birth defects affecting several organs. V stands for vertebral defects (spinal cord), A stands for anal deformities, C stands for cardiac problems, TE stands for tracheoesophageal fistula, R stands for renal abnormalities (urinary system and kidneys), and L stands for limb deformities (arms and legs).

VAD – Ventricular Assist Device: a medical-technological device supporting the heart and circulation, commonly known as "artificial heart"

Vascular – Pertaining to the blood vessels.

Vascular headaches – it is an abnormal stretching of the arterial walls in the cranium as a result of vessel – wall disease.

Vasoconstrictions – Narrowing of the blood vessels.

Vasodilatation – Dilatation of the blood vessels.

Vasodilator – agent that widens blood vessels.

Vein – Any one of a series of blood vessels of the vascular system that carries blood from various parts of the body back to the heart; returns oxygen-depleted blood to the heart.

Venous reservoir – collects venous return and stores excess volume; may be incorporated into the oxygenator system.

Ventilation – movement of air (gases) in and out of the lungs.

Ventricle – one of the two pumping chambers of the heart; right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery; left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta.

Ventricle (right and left) – One of the two lower chambers of the heart, either on the left or right.

Ventricular fibrillation – A condition, in which the ventricles contract in a rapid, unsynchronized fashion. When fibrillation occurs, the ventricles cannot pump blood throughout the body.

Venule – A small vein; especially one of the minute veins connecting the capillary bed with the larger systemic veins.

Vertebral Column (or spinal column or spine or backbone) – Flexible column extending the length of the torso.

Vesico ureteral reflux (VUR) – the abnormal flow of urine from the bladder back into the ureters; often as a result of a urinary tract infection or birth defect.

Vibration – A shaking massage technique; a fine tremulous movement made by the hand or fingers placed firmly against a body part and causing that part to vibrate. Often used for a soothing effect; may be stimulating when more energy is applied.

Villi is a plural of villus, which is a thin projection from a surface. The term in development is used to describe the individual functional units together of the fetal placenta.

Villi, primary (primary chorionic villi) is a term describing the earliest stage of embryonic placenta development. In humans, the conceptus during week two this first stage of chorionic villi development consists of only the trophoblastic shell cells (syncitiotrophoblasts and cytotrophoblasts) forming finger-like extensions into maternal decidua. Initially these finger-like projections cover the entire surface of chorionic sac and later become restricted to the placental surface. The villi stages are ongoing as the placenta continues to grow through both the embryonic and fetal development. Placental villi stages are primary villi, secondary villi and tertiary villi.

Villi, secondary (secondary chorionic villi) is a term describing the second stage of embryonic placenta development. In humans, the conceptus during week 3 onward this stage of chorionic villi development consists of the trophoblastic shell cells (syncitiotrophoblasts and cytotrophoblasts) filled with extraembryonic mesoderm forming finger-like extensions into maternal decidua. Initially these finger-like projections cover the entire surface of chorionic sac and later become restricted to the placental surface.

Villi, tertiary (tertiary chorionic villi) is a term describing the final stage of embryonic placenta development. In humans, the conceptus after week 3 the chorionic secondary villi now develop placental blood vessels within the core extraembryonic mesoderm. The villi form finger-like extensions that are either anchoring chorionic villi attached to the maternal decidua or floating chorionic villi in maternal lacunae. The villi stages are ongoing as the placenta continues to grow through both the embryonic and fetal development.

Villitis, chronic – It can occur following placental infection leading to maternal inflammation of the villous stroma, often with associated intervillositis. The inflammation can lead to disruption of blood flow and necrotic cell death.

Viscoelastic properties – The property of a material to show sensitivity to rate of loading.

Vital Capacity – Maximum volume that can be exhaled after taking the deepest breathe. VC = TV + IRV+ ERV.

Volt – The electromotive force that must be applied to produce a movement of electrons.

Voltage sensitive permeability – The quality of some cell membranes that makes them permeable to different ions based on the electric charge of the ions. Nerve and muscle cell membranes allow negatively charged ions into the cell while actively transporting some positively charged ions outside the cell membrane.

Volume contraction is a decrease in body fluid volume, with or without a concomitant loss of osmolytes.

Volvulus – a twisting of the stomach or large intestine that leads to blockage of the digestive tract.

Vomiting – the release of stomach contents through the mouth; also known as throwing-up.

Water intoxication is a process of consuming too much water too quickly.

Waveform – The shape of an electrical current as displayed on an oscilloscope.

Wave length – The distance from one peak to the next; energy from electromagnetic radiation is inversely proportional to its wave length.

White matter – Nervous tissue in the brain and spinal cord that contains myelinated axons. Compare with gray matter.

Winter's formula is used to evaluate respiratory compensation when analyzing acid-base disorders and a metabolic acidosis is present. It can be given as

$$P_{CO_2} = \left(1.5 \times HCO_3^-\right) + 8 \pm 2$$

where HCO_3^- is given in units of mEq/L and PCO_2 will be in units of mmHg. Winter's formula gives an expected value for the patient's PCO_2; the patient's actual (measured) PCO_2 is then compared to this. If the two values correspond, respiratory compensation is considered to be adequate. If the measured PCO_2 is higher than the calculated value, there is also a primary respiratory acidosis. If the measured PCO_2 is lower than the calculated value, there is also a primary respiratory alkalosis.

Xenograft valves – Artificial valves made from animal tissue are called xenografts. Most often the valves are made from pig aortic valves. More recently, some valves have been made from cow tissues.

X-ray – a diagnostic test, which uses invisible electromagnetic energy beams to produce images of internal tissues, bones, and organs onto film.

β-endorphin – A neurohormone derived from β-lipotropin and containing enkephalin. It is similar in structure and properties to morphine. β-endor- phin has a half-life of 4 hours.

β-lipotropin – A pituitary hormone containing β-endorphin and enkephalin and having opiate activity.

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