ENGINEERING IN MEDICINE & BIOLOGY

George D. O'Clock

Electrotherapeutic Devices

PRINCIPLES, DESIGN, AND APPLICATIONS

Electrotherapeutic Devices

Principles, Design, and Applications

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Preface

A number of motivating factors contributed to the development of the material in this book. Many professionals in medicine, biomedical engineering, and biophysics have expressed the concern that electrotherapy literature often does not have enough science incorporated into the material. There are many good biomedical engineering and biophysics textbooks available that address a wide range of topics in physiology, immunology, the cardiovascular system, the renal system, the endocrine system, imaging, conventional therapy, and so on. The level of rigor that one sees in these books, with respect to mathematics, physics, and chemistry, is often not found in those that address electrotherapy or magnetotherapy. In some cases, when science is incorporated, the material is often unclear, unconnected, or not adequately linked with applications. I hope that this book will satisfy some of those criticisms. You, the reader, will have the final word on whether this is an improvement, or not.

The material that follows should be useful in a variety of university undergraduate and graduate level courses, short courses, and continuing education courses in the fields of biomedical sciences, biomedical engineering, biophysics, and other related courses in the biological sciences. Mathematical analysis tools requiring the use of calculus do appear in a few places. For the most part, however, the mathematical content is primarily limited to the algebra level.

Another motivating factor for this book involves the very foundations of physiology and cell biology. Since the early 1900s, the basic building blocks for these subject areas have been focused on chemistry. A bit of physics is often thrown in, but chemistry has been the primary element in laying the foundation. This is why our understanding and modeling of biological systems is often so vague and limited. Chemistry without physics is like Dick without Jane.

Chemistry can be used to model cellular and physiological systems up to a point. However, many of the deficiencies associated with accurately describing biological phenomena, characterizing health problems, and developing appropriate and safe therapeutic methods are due to a lack of appreciation and understanding of the basic principles of physics. This has been a significant problem in the field of medicine for almost 100 years, and these deficiencies have imposed serious consequences and costs in terms of money and lives.

The human body utilizes a wide array of electrical and electrochemical systems in metabolism, transport of vital materials, digestion, excretion, immune system response, healing, reproduction, information flow, and regulation. The electrical nature of biological systems goes right down into the cellular, subcellular, molecular, and atomic level. Electron transport and proton gradients in cell respiration are fundamental processes involved in the production of our energy currency, adenosine triphosphate (ATP). Many papers in scientific journals discuss ion and electron transport in biological tissues, electron and proton tunneling in proteins and nucleic acids, and charge accumulation. Negative and positive charge transfer between cell membrane receptor elements in immune system response has been described in scientific journals. The electroosmotic movement of water has been modeled as it relates to processes in wound healing and regulation. The heart, nervous system, and renal system are all hotbeds of electrical activity. In fact, the electrical activity associated with our cells can be used to calculate the amount of power (approximately 100W) associated with the human body engaging in normal activity. Electrical phenomena are responsible for a large part of what we do and how we feel. In fact, are you having problems sleeping? Well, first of all, get rid of the bedroom TV. Then, remove all of the wiring under, behind and beside your bed. Even without significant current flow, a nearby wire plugged into a wall socket can still produce a significant electric field. I can tell you from experience that those 60-Hz electric fields can make some of us sweat, disturb our sleep, elevate our blood pressure, and produce very vivid nightmares.

With all of these electrical processes in the human body, and the sensitivity of the human body to outside electrical activity, it stands to reason that both electrical and magnetic stimulation, if properly applied, would be useful in therapy. The fields of physics, biophysics, and physical chemistry verify that this is true. But something terrible happened in the last century that interfered with the proper blend of chemistry and physics in medicine. Over a 30-year time frame, a significant amount of technology and activity in the development and improvement of electrotherapeutic, magnetotherapeutic, and electromagnetic therapy devices and protocols was beaten down and obliterated. Within that 30-year time period, a significant amount of the progress made over the previous 100 years was either abandoned or destroyed. And, more often than not, the lives and fortunes of those involved were also destroyed. Daniel Haley's book,

Politics in Healing, provides an interesting and disturbing history of this particular process of abandonment and destruction. Barry Lyne's book, *The Cancer Cure That Worked*, is another good source of information. Read both books, and be prepared to become angry.

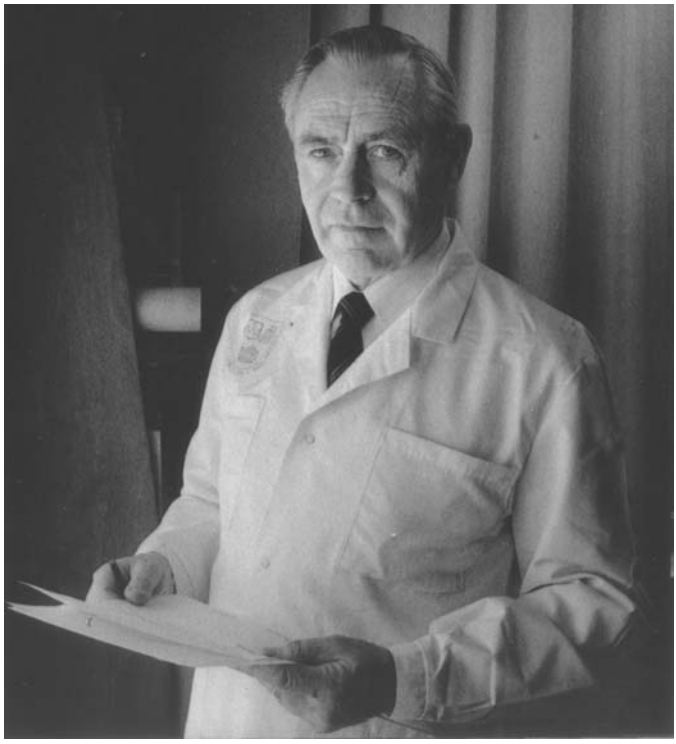
But no matter how many times certain segments of the medical profession try to subvert nonconventional therapies and new knowledge, they will not be successful in the long run. There are a number of reasons. One of them involves the intelligence, integrity, curiosity, and perseverance of dedicated medical doctors and scientists who refuse to be confined to outdated dogma and dangerous medical practices. This book will discuss the work of two of those dedicated medical doctors, Björn E. W. Nordenström, M.D., Ph.D., and Robert O. Becker, M.D. Their curiosity and integrity would not allow them to be restrained or confined by dogma and convention. Were it not for the likes of them, some of us would be very uncomfortable, debilitated, or dead by now. They are my heroes, and my standards. They deserve all of the respect, time, effort, and attention we can give them.

In the United States, for those who hold M.D. or Ph.D. degrees, the title "Doctor" is often preferred over the title "Professor." There are reasons for that, which I will not address here. In many countries outside the United States, however, those who hold M.D. or Ph.D. degrees often prefer the title of professor rather than the title of doctor. In those countries, the title of Professor is more respected and has more status. With the exception of the dedication, this book will follow the U.S. convention.

The author wishes to acknowledge helpful correspondence and discussions with the following individuals: Dr. Photios Anninos, Dr. Roger Burnell, Dr. Lyle Feisel, Dr. Jim Holte, Dr. Katsui Ito, Dr. John Jarding, Dr. Thomas Koval, Dr. Abraham Liboff, Dr. Mark Lyte, Dr. Nita Maihle, Dr. Marko Markov, Dr. Leland Michael, Dr. Ralph Moss, Dr. Björn Nordenström, Dr. Jörgen Nordenström, Dr. Paul Rosch, Dr. Daryl Schaefer, Dr. Demetrio Sodi Pallares, Dr. Stuart Taylor, Dr. A.L. Thomasset, Dr. Warren Warwick, Dr. Yu-Ling Xin, Carl Firley, Daniel Haley, John Jones, and Toby Leonard.

This book is dedicated to Björn E. W. Nordenström, M.D., Ph.D., professor emeritus in radiology, the former head of diagnostic radiology at Karolinska Institute (Stockholm), a member of the Nobel Assembly for Medicine (1967–1986), and the president of the Nobel Assembly for Medicine in 1985. His research efforts led to the theory of biologically closed electric circuits (BCEC) and to the development of Nordenström's Electrolytic Ablation Therapy–Electrochemical Therapy (NEAT-EChT).

Professor Nordenström had the unique ability to visualize and analyze what others could not see. He applied his results and theories toward the development of highly effective electrotherapeutic techniques in the treatment of



Dr. Björn Nordenström. (Courtesy of Björn E. W. Nordenström, M.D., Ph.D., professor emeritus in radiology, Karolinska Institute, Stockholm, Sweden.)

cancer and other diseases. The price he paid for his insights and contributions was often severe criticism and outright rejection by his colleagues.

Lives have been saved and the quality of life has been enhanced for many cancer patients who received the benefits of Björn Nordenström's ideas and his therapeutic techniques. After undergoing repeated chemotherapy and radiation therapy sessions, many cancer patients were told they could not be treated any further with conventional therapies. They were often written off and abandoned by the same medical doctors who criticized Professor Nordenström's theories and results. But Professor Nordenström did not write these cancer patients off, nor did he abandon them. Björn E. W. Nordenström gave many cancer patients hope and life—and that will be his legacy.

1

Introduction to Electrotherapy

1.1 Motivating Factors

When treatment choices are being evaluated for various diseases and health problems, there are often many therapeutic techniques and combinations that can be considered. Some of the accepted therapeutic techniques are quite simple and patient friendly; others are complicated and can even be dangerous. A 2003 *New England Journal of Medicine* article reported that, in U.S. hospitals, more than 100 patients die every day because of injuries from their care, not from their diseases [1]. But that number may be very conservative.

An article in the July 26, 2000, *Journal of the American Medical Association* indicated that medical doctors are the third leading cause of death in the United States, contributing to approximately 250,000 iatrogenic deaths every year [2]. Iatrogenic disease is defined as a heath problem, or complication, that is a result of an examination, diagnostic procedure, or treatment administered by a physician, surgeon, or medical facility. The information in Table 1.1 indicates that the number of deaths due to medical mistakes may be much higher [3]. And yet, the information shown in Table 1.1 may still be too conservative!

If only 20% of fatal medical errors are actually being reported, as indicated by [2], the number of deaths in U.S. hospitals and clinics due to iatrogenic disease could be close to 1 million per year! In this case, medicine and medical practitioners appear to be the leading cause of death in the United States. Some members of the medical community have attacked these conclusions and described them as nothing more than "doctor-bashing" and the results of faulty analytical techniques. However, an examination of the sources will reveal that the data and conclusions are all derived from respected medical journals and government reports. Doctor-bashing is definitely not the problem here.

Table 1.1
Patient Deaths Due to Iatrogenic Disease

Number of Deaths Estimated Due to Medical Errors	Source
100 patients per day (injuries)	[1]
180,000 patients per year	[2]
250,000 patients per year	[3]

Even so, we need to be careful, because statistics and numerical analysis do not reveal the entire story. Iatrogenic disease death statistics are not as much of a reflection of medical doctor incompetence as they are of poor health care system design. The iatrogenic disease problem appears to be exacerbated by the complexity and dangers of the diagnostic tools and therapeutic combinations that medical doctors are required to consider and use. For example, many drugs used to treat cancer and some neurological diseases are highly toxic. They are so toxic that an apparently safer alternative, arsenic, has been reintroduced in cancer therapy [4]. For certain types of cancer, the U.S. Food and Drug Administration (FDA) has approved the use of this old remedy. Arsenic appears to be less toxic and more effective in treating certain types of leukemia when compared with many of the standard chemotherapeutic agents.

We might wonder: Are there any therapeutic alternatives available that can be effective and patient friendly without the burdens of high toxicity, high cost, high risk, and terrible side effects? For many diseases and other health problems, the answer is yes. *Electrotherapy* has shown excellent results in applications where conventional therapeutic techniques fail. The electrotherapeutic alternative has a long history of success, and it has been available for more than 150 years. Using appropriate treatment protocols, electrotherapy can provide excellent therapeutic efficacy, with minimal patient discomfort, minimal (or no) side effects, and consistent results with repeat treatments. Electrotherapy can be administered in combination with many other standard therapeutic techniques. Electrotherapy offers a safe method of treatment at a much lower cost compared with other treatment options.

In the early 1900s, as Western medicine began to lose its appreciation and understanding of physics and concentrated more on chemistry, electrotherapy fell by the wayside in conventional medical practice. Electrotherapy continued to be applied for cases of visual system disease and certain neurological disorders. Medical practitioners who were engaged in wound healing and physical therapy continued to publish clinical research results involving electrotherapeutic techniques. But within the first 30 years of the twentieth century, drugs, radiology, and surgery became the dominant forces in Western medical practice and

dogma. Doctors who provided certain electrotherapeutic services were ordered to stop. Many electrotherapeutic practices were abandoned, research and development laboratories were closed, and some electrotherapeutic devices were destroyed.

Since that time, those who adhere to allopathic medical dogma appear to have lost touch with the fact that many processes in the human body are governed by electrochemical or electrical mechanisms. Electrotherapeutic techniques support what the biological system (the human body) is already doing. The application of external (exogenous) voltages, electric fields, and currents can be beneficial in many cases where the biological system's natural electrical and electrochemical healing and regulatory processes require some assistance. This kind of outside assistance, using appropriately designed electrotherapeutic devices and protocols, is the essence of electrotherapy.

Electrotherapy can be used as a complementary or adjunct modality to assist the human body's normal electrochemical and electrical processes that support healing, regulation, and development. Electrotherapy offers significant advantages over many conventional therapies when one considers the combination of effectiveness, absence of harmful side effects, low cost, safety, reliability, reproducibility, compatibility with other therapeutic techniques, and ease of application.

1.2 Electrotherapeutic Device—Technique Overview

Electrotherapy involves a wide range of techniques and devices. This book will concentrate on electrotherapeutic techniques that administer electric currents, voltages, and electric fields to specific regions of the body for applications in a number of strategically important health problems. The primary focus will be on wound healing, cancer, visual disease, and connective tissue disease.

An electrotherapeutic device can be described as an electrical source or electrical signal generator, combined with a specific set of electrodes or probes, that will stimulate or inject a static (direct current, dc) and/or time-varying (alternating current, ac, or pulsed) electrical signal into living tissue. Each health problem or disease will generally be sensitive to specific waveform shapes, frequencies, modulation formats, output current levels, current-voltage variation limitations, tolerances, duration of application, safety requirements, and treatment protocol requirements that are considered optimal for the specific condition being treated.

In some cases, the application of a static or time-varying electric potential or electric field (with an associated current and current density) will be the preferred therapeutic method. In other situations, a static or time-varying magnetic field (with its induced electric field, and associated current and current density)

may be preferred. And there are times when the preferred therapeutic technique will utilize an electromagnetic field. Comparisons between electrotherapy and magnetotherapy will be addressed in Chapter 4.

If the electrotherapeutic device uses a probe or electrode to make direct contact with body tissue (Figure 1.1), the magnitude of the resulting current is a function of the voltage being applied, the probe-tissue interface parameters, and the electrical impedance of the tissue.

In some applications, the electrotherapeutic device may not be in direct contact with the body. The electrotherapeutic effect may involve an interaction between an applied electric field, or electromagnetic field, and various tissues and organs. In this case, the resulting electric flux density, induced voltages, charge accumulation, and current response will be dependent upon a number of tissue and organ parameters including dielectric constant, conductivity, fluid content, and biological structure. Also, using either direct contact or indirect coupling of electric or electromagnetic fields with tissues and organs, the

(a) (b)

Figure 1.1 A macular degeneration patient being treated with a TheraMac electrotherapeutic device. The average electrical currents applied are in the range of 50 to 150 μA. (a) One of the conductive probes is pressed against the patient's closed eyelid, and the other probe is held in the patient's hand. Although several electrotherapeutic treatments may be required before significant improvements in visual acuity occur, many macular degeneration patients report that one of the first improvements they notice is a significant reduction in the "haze" or "fog" that is present in their peripheral vision. Some patients notice significant improvements in color vision after receiving several treatments. (b) Treatment is given with eyelids closed, but this photograph has been taken with the patient's eyes open during treatment to show the patient looking away from the probe position for best access to the macula. (Courtesy of John Jarding, O.D., Acuity Medical, Brighton, Michigan. Also, see [5].)

underlying bioelectric mechanisms have properties that are often nonlinear, anisotropic and time-varying.

For clarity, such terms as "current," "voltage," "electric field," and "power" should be defined. Some of the following information will appear in subsequent chapters. Imagine two metal plates suspended in a vacuum. One plate is connected to the positive terminal of the battery and the other plate is connected to the negative terminal of the battery. The region between the plates now has an electric field, E (in volts per meter), that is equal to the voltage (or potential) applied between the plates, divided by the distance between the plates, d. So, $E = V/d$. If an ion with a positive charge, q (in coulombs), is placed between the plates, there will be a force on the positively charged ion, F, that will move the ion in the direction of the negative plate, $F = qE = q(V/d)$. Under the influence of the electric field, the positively charged ion with mass m will accelerate, a, according to the well-known relationship, $F = ma$. This moving ion can be thought of as a basic element of an electric current. Now we can look at what happens when a group of charged particles with total charge Q are influenced by the application of a potential or an electric field. Electric current, I (in amps), is defined as a change of total charge, ΔQ, divided by a change of time, Δt (in seconds), or $I = \Delta Q/\Delta t$. Therefore, if there is any movement or change over time associated with a collection of charged entities or carriers, this movement or change over time, by definition, is an electric current. The charged carriers can be electrons, ions, or charged molecules.

The change in charge with respect to the change in time can involve the movement of charged particles in one direction. This kind of current is often called a *drift current*. In this case, the collection of charged particles has an average velocity, or *drift velocity*, in one direction. The drift velocities associated with ions in solution, and electrons in wires, are surprisingly slow. Chapter 2 (and Exercise 2 in Chapter 3) will go into more detail on the velocities associated with charged carriers in solution, in tissue, or in conventional conductors. Charged carrier motion in one general direction is the essence of direct current. Direct current is the kind of current that is associated with a conventional flashlight.

In some cases, the charge carrier does not continue to move in one direction; it may alternate in its direction of motion in a continuous (sinusoidal – alternating current), pseudo-continuous (triangular, sawtooth, and so forth), or discrete (pulsed) manner. This kind of charged particle motion is related to the displacement current concept, and it is the kind of alternating or time-variable current that is available from a wall socket (sinusoidal), a highway flasher (sawtooth), or a computer memory (discrete pulses). So for dc, ac, pseudo-continuous, and pulsed currents, the change of charge with respect to time can involve changes in position or location that are continuous, somewhat continuous, or relatively abrupt.

Another kind of current is associated with variations in charged carrier concentration and charged carrier energy distribution over a short distance. This kind of current is called diffusion current. It is a type of current associated with semiconductor P-N junctions and the base region of bipolar transistors.

The two kinds of current that will be relevant for the material in this book are dc and ac currents. Many authors insist that an ac current and ac voltage waveforms require a sinusoidal waveform shape. Most of the alternating currents discussed in this book will be discrete, or pulsed, waveforms rather than the conventional ac waveforms that are continuously changing in a sinusoidal fashion. As far as I am concerned, the continuous sinusoid, pseudo-continuous, and the discrete pulse are all alternating.

The voltage between the two previously mentioned plates can be provided by a battery, which produces a potential between two electrodes through chemical activity. Positive charges will tend to flow from the positive region to the negative region. Negative charges will tend to flow from the negative region to the positive region. The movement of these charges, or the charge flow, is the current, I. The current density, J, associated with the change or movement of these charges is defined as the current, I, divided by the cross-sectional area, A, that the charges traverse, $J = I/A$.

Considering a current, I, flowing through a resistance, R, with a voltage, V, across the resistor, the power, P, associated with this movement of charge is the product of the current times the voltage, $P = I \times V$. From Ohm's law, we know that $V = I \times R$. Therefore, the power dissipated in the resistor is $P_D = I^2 \times R$.

1.3 Assessment, Versatility, Acceptance, and Therapeutic Efficacy of Electrotherapy

In the treatment of wounds, cancer, visual disease, fractures, connective tissue disease, and certain neurological disorders, electrotherapy has proven itself to be one of the most efficacious therapeutic modalities available. The origins of electrotherapy in wound healing date back to the 1600s when healing mud and saltwater combinations were used to treat skin disorders. Electrically charged gold leaf was used in the 1700s and 1800s to prevent smallpox scars. More recently, several studies using direct current for wound healing on patients were reported by Assimacopoulos [6] and Wolcott et al. [7]. Direct currents of 200 μA to 1 mA were used to treat chronic leg ulcers and ischemic skin ulcers. A paper on wound healing in a 2001 issue of the *Archives of Physical Medicine and Rehabilitation* [8] reported that a high-voltage (~50V) electrical stimulation device provided significant healing improvements for 65% of patients treated,

while only 35% of the patients in the placebo group were able to show progress in healing.

One of the benefits of using direct currents to treat wounds noted by many health care practitioners is that the electrotherapeutic treatment has a tendency to mitigate contamination by microbes [9]. The wound sites are often sterile after several days of treatment using direct currents at the microamp (μA) level.

According to the U.S. Department of Health, electrotherapy has been very effective in a variety of wound healing applications. Clinical practice guidelines issued by the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality strongly recommend electrical stimulation, or electrotherapy, as the only adjunctive therapy to enhance healing of recalcitrant and refractive pressure ulcers [10]. Blue Cross of California's Medical Policy Number 2.02.04 indicates that the supervised use of electrical stimulation may be considered medically necessary as a treatment for certain types of pressure ulcers, arterial ulcers, diabetic ulcers, and venous stasis ulcers when a 30-day trial of initial wound healing management has failed.

The benefits of electrotherapy reach far beyond wound healing. For many years, ophthalmologists have been telling patients afflicted with macular degeneration and retinitis pigmentosa that there is no treatment for their visual disease. That conclusion, however, has not been true for more than 130 years. In fact, during the nineteenth century, medical doctors (including ophthalmologists) pioneered the application of electrotherapy for various visual system health problems [11, 12]. One of the earliest records for the successful use of electrotherapy to treat visual system disease dates back as far as 1801 [13]. Some of the first electrotherapy papers published for the treatment of retinitis pigmentosa appeared in monographs and ophthalmology journals in the mid to late 1800s [14–17]. These treatments (described as a form of galvanotherapy) often involved relatively high levels of dc using wet cell batteries as the source. At that time, some medical doctors mentioned consistency problems with galvanotherapy treatment results. They indicated the current intensity levels that were being administered to patients appeared to be much too high. And they were right.

In Figure 1.1, a macular degeneration patient is shown receiving electrotherapy. With eyelids closed, one electrode is placed at various locations within the orbit of the eye and the other electrode is held in the patient's hand. Average currents in the range of 50 to 150 μA are administered. The combination of results from an FDA double-blind clinical trial (Feasibility Phase), a 34-patient study, and a 404-patient Institutional Review Board (IRB) study [5, 18] gave significant support for the therapeutic efficacy of electrotherapy in the treatment of dry macular degeneration. Information sheets summarizing the study results indicate that, depending upon the level of current used, 26% to 61% of the patients treated show a two-line or better enhancement in visual

acuity on the Snellen chart after being treated over a relatively short period of time. Approximately 6,500 treatments were administered for 450 patients. Follow-up results indicate that patients gained or maintained visual acuity for periods between 2.5 and 4.5 years. Some patients have maintained a significant level of visual acuity for periods of 7 to 12 years, and a number of them are still able to pass the vision test for their driver's license.

The benefits of electrotherapy are not just confined to wound healing, treatment of diseases of the visual system, and pain mitigation. The application of direct current to needle electrodes (galvanopuncture) has been used to treat aneurysms as early as 1849 [19]. Also, electrotherapy has been very effective and relatively consistent in the treatment of malignant and nonmalignant tumors. Electrotherapeutic techniques that destroyed malignant tumors with localized high-frequency alternating current spark techniques were under investigation in the early 1900s [20]. This approach was developed as a result of eighteenth and nineteenth century reports of tumor remission by lightning strike survivors. An extension of the galvanopuncture technique, shown in Figure 1.2, has been developed and successfully utilized by Dr. Björn Nordenström to treat breast and lung tumors [21–23].

Medical doctors in China, Australia, Sweden, and Germany have demonstrated that Nordenström's electrotherapeutic technique can be very effective in treating localized tumors (both malignant and nonmalignant) [24–28]. Figures 1.3 and 1.4 provide an indication of how effective electrotherapy can be in treating cancer [24, 29].

Using Nordenström's NEAT-EChT electrotherapeutic technique, Table 1.2 indicates that the 5-year survival rate statistics achieved by the Chinese for advanced-stage cancer patients are significantly better than the 5-year survival rate statistics achieved in the United States using conventional chemotherapy, radiation therapy, and surgery. The NEAT-EChT technique can be

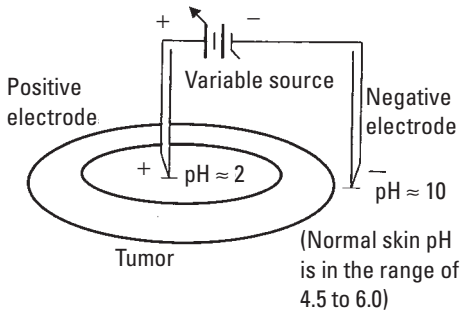
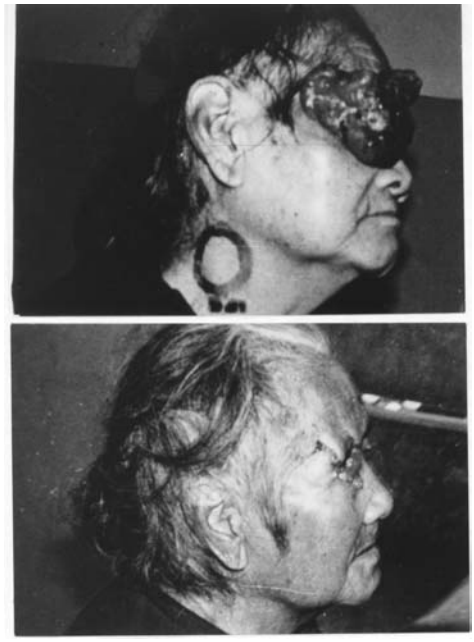


Figure 1.2 Nordenström's electrolytic ablation therapy–electrochemical therapy (NEAT-EChT) method, offering improvements over standard galvanopuncture techniques, for the treatment of malignant and nonmalignant tumors.



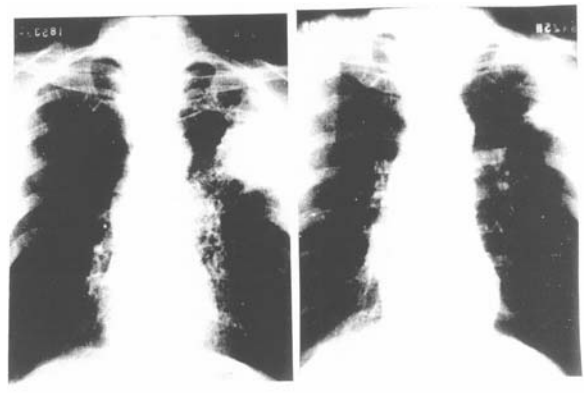
Before electrotherapy treatment

After electrotherapy treatment

Figure 1.3 A paper, coauthored by Dr. Yu-Ling Xin (Chief of Thoracic Surgery, China-Japan Friendship Hospital, Beijing) and delivered by Dr. C. K. Chou (formerly City of Hope National Medical Center, Duarte, California), electrified the audience at the 15th Annual Bioelectromagnetics Society Meeting held in Los Angeles in 1993. Dr. Xin treated his cancer patients with an electrotherapeutic technique developed by Dr. Björn Nordenström (formerly Head of Diagnostic Radiology, Karolinska Institute, Stockholm). These photographs show the progress of one of Dr. Xin's patients, a 73-year-old woman with a recurrent squamous cell carcinoma. The tumor size, before treatment, was 9.5 cm × 14 cm. After three treatment sessions, the tumor disappeared. In the after-treatment photograph, most of the scarring and red tissue around the region of her right eye occurred with previous surgeries that attempted to remove the recurrent tumor. After electrotherapy was administered, no tumor recurrence problems were detected in 4 years of follow-up visits. (Courtesy of the IABC Foundation and Dr. Yu-Ling Xin, China-Japan Friendship Hospital, Beijing.)

administered alone, in combination with low-dose chemotherapy, or in combination with low-dose radiation therapy. In addition, NEAT-EChT does not develop any significant resistance in response to multiple treatments, as is often the case with radiation therapy and chemotherapy.

Electrotherapy has also proven to be very effective in treating fractures that will not heal by conventional means [30, 31], treating connective tissue injury [31, 32], treating sleep disorders [33], and mitigating depression [34].



(a) (b)

Figure 1.4 (a) Tumor at the upper left lobe (upper right in the X-ray image) for a 52-year-old male lung cancer patient. The tumor size was 9.5 cm × 11.0 cm. Needle biopsy revealed squamous cell carcinoma. The patient was not a candidate for surgery chemotherapy or radiation therapy because of a chronic obstruction, pulmonary disease, and coronary heart disease. Six platinum electrodes were inserted through the skin, into the tumor mass, using X-ray monitoring, and electrotherapy was administered. (b) The tumor completely disappeared 6 months after receiving his final electrotherapy treatment. The patient's progress is very good. He has had a check-up every year, and follow-up has been ongoing for 10 years. (Photographs courtesy of Dr. Yu-Ling Xin, China-Japan Friendship Hospital, Beijing, and the IABC Foundation, Palm City, Florida. Also refer to http://www.iabc. ReadyWebsites.com.)

Table 1.2
Comparison of Types of Cancer and 5-Year Survival Rates in China (Using Nordenström's NEAT-EChT Electrotherapeutic Technique for Cancer Treatment) and the United States (Using Combinations of Conventional Cancer Therapeutic Techniques)

	China	**United States**
	(Using NEAT-EChT alone, and with low-dose chemotherapy and herbal therapy)	(Chemotherapy, radiation therapy, and surgery) (National Cancer Institute SEER Cancer Statistics Review)
All cancers	66% (Stage I and II) 45% (Stage I, II, and III)	62% (Stage I and II) (U.S. statistics heavily weighted with Stage I categories)
Middle and late-stage lung cancer	≥ 28.4%	12.6% to 22% (depending upon age)
Liver cancer	15%	< 6%

Electrotherapy appears to offer some possibilities for HIV/AIDS treatment. Kumagai and his colleagues have discovered that certain types of HIV-1 infected cells (P6 HeLa) are much more sensitive to electrical stimulation (1V dc for 30 minutes) than uninfected cells. Approximately 87% of the infected cells were damaged, and only 4% of the uninfected cells were damaged [35, 36].

The influence that electrotherapy can have on structure and function in the human body is evident from the in vitro, in vivo, and in situ work that has been done in various research laboratories. The chapters that follow will go into more detail on these results and their implications for therapy. However, the importance of those results and their influence can be mentioned here. Cell morphology, microfilament structure, and enzyme structure can be affected by electrical stimulation, and this activity can have significant effects on cell proliferation, cell migration, metabolic activity, and immune function. Both normal and malignant cell proliferation can be changed significantly with the application of low-level electric currents, and this has profound implications for cancer therapy. For tissue generation/repair and wound healing, keratinocytes (epidermal cells) will migrate under the influence of electric fields (galvanotaxis), and fibroblast (dermal cell) proliferation is enhanced with electric fields as low as 1 mV/m and current densities at or below 130 μA/cm^2. The application of 30-mV potentials can move macromolecules and cell membrane receptors. This activity can influence the binding of ligands to receptors and can affect cell-signaling pathways for metabolic processes, cell proliferation, and immune function. The effects of electric fields on cyclic adenosine monophosphate (cyclic AMP) production can influence kinase activity, cell structure, and function. Gene expression, calcium influx, and adenosine triphosphate (ATP) levels can be varied by the application of electric fields and low-level electric currents. Ca^{++} influx into the cell's cytoplasm can be varied with electric or magnetic fields. This can influence a large number of processes including ATP production, protein kinase activation, transcription, cell metabolism, cell proliferation, cell death, secretion processes, muscle relaxation-constriction, and blood vessel dilation-vasoconstriction (important in blood pressure regulation). It becomes clear that electrical stimulation can have significant influences on many of the structures, substances, functions, and processes involved in cellular activity from the birth of the cell to its death (i.e., apoptosis or necrosis).

1.4 The Evolution of Electrotherapy in the Face of Medical Dogma

Electrotherapy has been applied as a therapeutic option to address a number of health problems for more than 3,000 years. The ancient Greeks and Romans used the 50-V potential of a torpedo fish (electric eel) to treat gout, certain muscular deficiencies, paralysis, and headaches [37, 38]. In the early 1700s, a

precursor to the electric defibrillator was developed by Kite [39], and one or two successful cardiac resuscitations supposedly did occur. Also, at that time, the Leyden jar capacitor was used to treat paralysis and pain. Often, the voltages and currents utilized in early electrotherapeutic applications were much too high and many patients suffered a relapse [39].

In the 1800s, more rigor and care were coupled with electrotherapeutic clinical research efforts, and the applied currents and voltages were reduced. The enhancement of wound healing by electrotherapeutic means was introduced and inspired by the work of many, including Galvani, Aldini, Matteucci, and du Bois-Reymond. Differences in electrical potential were measured between wound sites and the surrounding normal tissue [40]. Electrical currents were measured in the vicinity of fresh wounds, and it was discovered that an injured bleeding finger is electrically positive compared with the uninjured finger. By 1990, the work of Becker, Burr, Lund, and Nordenström demonstrated that biological entities have unique electrical equilibrium conditions and specific electrical responses to disease and injury [41–44]. They describe certain electrical currents, voltages, and charge accumulation conditions as being associated with health, and others as being associated with disease or injury [45]. Their work strongly indicates that the endogenous electrical processes associated with healing can be assisted, or enhanced, with exogenous sources of electrical stimulation (electrotherapy). The results of almost 200 years of research in the electrical characteristics of living systems provide valuable insights for improvements in the application of electrotherapeutic techniques in the treatment of a variety of diseases and health problems.

There is another individual who comes to mind, and he has written a number of papers on electrotherapy. His views and explanations are very informative and very interesting. I am referring to Dr. Tim Watson of the Department of Allied Health Professions, Physiotherapy, University of Hertfordshire, United Kingdom. His Internet Web site is http://www.electrotherapy.org.

Citing the work of others, Dr. Watson provides an interesting overview concerning the relationship between endogenous electrical activity, injury, and healing [46]. He presents three main themes: (1) the endogenous electrical activity of the body can be used as an indicator of a particular pathological process without necessarily attributing a cause/effect relationship; (2) the endogenous electrical activity of the body acts as an initiator, control mechanism, or modulator of the post-embryonic growth and healing process; and (3) by enhancing the endogenous electrical activity of the damaged tissues [I believe Dr. Watson is referring to the use of an exogenous (external) source of electrotherapeutic stimulation], the growth and/or healing process can be stimulated or enhanced. Similar themes are presented in this chapter and Chapter 2, but I like Watson's concise summary of those ideas. If you read the first two chapters of his Ph.D. dissertation [47], you will see the inspiration for certain parts of Chapter 2 in

this book. The models Dr. Watson uses, and his interpretation of the work of other researchers, provide some of the tools that are helpful in relating Nordenström's work in the electrotherapeutic treatment of cancer with the various electrotherapeutic techniques utilized in wound healing. After reading Chapter 3 of this book, I would recommend reading the material that Watson has published and has made available on his Web site (http://www.electrotherapy.org).

Up until the early 1900s, medical practitioners understood the principles of physics and chemistry and were able to incorporate those two areas of science into medical dogma and practice. A number of unfortunate events occurred in the early twentieth century that caused the medical profession to become focused on chemistry at the expense of physics. At that point, the range of therapeutic alternatives in medicine started to become quite limited, concentrating primarily on surgery, radiation, and drugs. Most of the early work associated with electrotherapeutic alternatives was abandoned. By the early 1970s, however, it was becoming obvious that many surgical, radiological, and pharmaceutical alternatives were dangerous, expensive, and not very effective. At that point, some medical practitioners started to reconsider electrotherapy.

Ellen Kuhfeld (Bakken Library, Minneapolis, Minnesota) wrote an interesting history of electrotherapy in the *1997 Proceedings of the Fourth International Symposium on Biologically Closed Electric Circuits* [39]. Early in her paper she writes a tribute to the efficacy of electrotherapy: "Electricity can do things a rational medicine would seize upon and treasure." In this one statement, Kuhfeld not only praises the benefits of electrotherapy, but she strongly hints of the single most destructive and constraining aspect of modern allopathic medicine—that is, its dogma.

The power and influence of medical dogma is interesting, and at times it can be frightening. In 1628, William Harvey published the results of his research, which indicated that blood circulated in the body at a very high rate [48]. Harvey's results also refuted the common belief that blood was consumed as fuel by the body to produce energy. The reaction to Harvey's denial of medical dogma was swift and violent. Harvey was threatened and harassed by his colleagues, his apartment was ransacked, and valuable research notes and papers were stolen. For speaking the truth, Harvey faced the violence, wrath, and insanity that are characteristic of a religious inquisition. In order to defend himself from potential attack, Harvey chose to carry a dagger.

In 1846–1847, a Hungarian-Austrian physician, Ignaz Semmelweis, introduced a hand-washing protocol in an obstetrical clinic. Part of the motivation for this procedure came from his observations that mortality rates among women who were treated by doctors and medical students were much higher than mortality rates for women who were treated by midwives. In the various clinics that used his hand-washing protocol (using a chlorinated lime solution)

the mortality rate was 6 to 14 times lower compared with clinics that did not use the antiseptic hand-washing protocol. In 1867, a British surgeon, Joseph Lister, introduced the idea of sterile surgery by recommending the use of carbolic acid to wash hands, sterilize surgical instruments, and clean wounds. Lister gave credit to the influence of Semmelweis. Both men faced harsh criticism from other doctors. Their protocols involved "too much work" and their ideas conflicted with the medical dogma of that time involving the "imbalance of humors." In spite of the obvious successes that occurred with the implementation of his antiseptic protocols, Semmelweis was ridiculed and finally fired from his position. In 1865, after what appeared to be a nervous breakdown with behavioral outbursts, Semmelweis was committed to a private asylum in Vienna. During one of his outbursts in the asylum, Semmelweis was beaten and subsequently died of his injuries. Lister lived long enough (he died in 1912) to see his recommendations incorporated into medical practice. However, long after the end of the U.S. Civil War, surgeons still smoked cigars while performing amputations.

Approximately 302 years after Harvey, and 65 years after Semmelweis, not much had changed in the response of the medical profession to new ideas and more effective therapies for patients. In the 1930s, under the direction of Dr. Morris Fishbein [49], the American Medical Association's (AMA) effort to destroy documents, clinical research records, equipment, and the reputations of people participating in certain types of electrotherapeutic and electromagnetic therapy techniques was relentless. The amount of violence, document theft, apparent murder (by poisoning), and equipment destruction that occurred represents one of the darkest chapters in the history of modern medicine [49].

Historical records have shown that new knowledge and improvements in diagnostic and therapeutic techniques are often not viewed in an objective and rational manner by modern medicine, and they are not easily introduced or accepted within the medical mainstream. Based on the experiences of William Harvey and many others, any threat to the dogma, power structure, and revenue structure of medicine will often be met with a violent and destructive response. Even today, Harvey's advice to us might be, "If your ideas threaten the established dogma and power of the medical profession, carry a dagger and be prepared to use it."

1.5 Summary

The complexity and dangers of the diagnostic tools and therapeutic combinations that medical doctors are required to use appear to be dominant factors in the disturbing reports of death and debilitation that occur because of iatrogenic disease. Statistics (which often appear to be understated) provide hard evidence

that the medical profession must question its own dogma more frequently and be open to implementing safer diagnostic and therapeutic techniques in the practice of medicine.

As previously mentioned, the critical comments in this chapter (and in the rest of the book) concerning the medical profession are definitely not associated with any form of doctor-bashing. Many similar comments and experiences have been reported by medical doctors themselves. The May 1, 2006, issue of *Time* magazine "What Doctors Hate About Hospitals" [50] reveals the experiences of those medical professionals. The question is asked: "What scares doctors?" And the answer is: "Being the patient." The article has a reasonable balance in that it mentions the problems that medical doctors have with complex technology, the vast amount of new information they need to absorb, new and complicated techniques and procedures, patient attitudes and communication, the business side of their practice, and the changing legal environment. Many techniques and procedures that M.D.s are forced to use are very unforgiving with respect to mistakes. However, the frank comments from many of the medical doctors quoted in this article are damning. One medical doctor commented on his wife's hospitalization experiences: "Not one day passed—not one—without a medication error. The errors were not rare; they were the norm."

Apparently, this experience is fairly common and well known by many medical professionals. For example, the article quoted a medical doctor who is also a distinguished professor of medicine. He was with his wife while she was hospitalized. This medical doctor was too frightened to leave his wife's bedside. He told another M.D., "I felt that if I was not there, something awful would happen to her. I needed to defend her from the care." Note that this is a statement from a medical doctor who teaches medicine in a prestigious university hospital! I rest my case.

It is obvious that medical practitioners are in desperate need of therapeutic alternatives that are much less complex, lower in cost, more effective, and more forgiving than the ones they have at present. Electrotherapy has proven itself to be an excellent stand-alone or adjunct treatment for a large number of health problems. Based on a wide range of successful in vitro, in vivo, and clinical studies, for many health problems and diseases, electrotherapy appears to be the answer to the prayers of many health care practitioners, patients, and insurance companies. As an example, electrotherapeutic and magnetotherapeutic techniques and protocols are often the only choice available to treat certain kinds of ulcers and fractures that will not heal by conventional means.

However, the introduction of electrotherapy will have its price and its consequences within the medical profession. In order to accept therapeutically efficacious, low-cost, and low-risk electrotherapeutic techniques and protocols into medical practice, medical doctors are going to have to be as familiar, and as well grounded, in physics and interconnected biological control systems as they are

in chemistry and anatomy. The medical profession is going to have to go beyond the lifeless cadaver in its anatomy focus. Medical doctors will have to become more dynamic in their thinking and recognize how the body is actually designed. Medical doctors will require more realistic models of how biological systems function. They will require a better grasp of the relationships between biological structure and biological function. The "Body Electric" [37, 41] and its associated electrical-electrochemical control systems [43, 44] will have to become a primary component of medical dogma.

And what will compel the medical profession to do this? A number of motivating factors come to mind, including skyrocketing medical care costs, increasing risks and the litigation costs (in both time and money) that often accompany risky procedures, the welfare of their patients, their consciences, the influence of medical doctors who dare to question, and the Hippocratic oath.

Exercises

1. Are we willing to accept the numbers given in Table 1.1, along with the estimate of 1 million iatrogenic disease related deaths per year (assuming that only 20% of fatal medical errors are being reported)? Statistics like these should be verified, or at least reevaluated. (a) Investigate to determine the total number of iatrogenic disease-related deaths per year from (1) adverse drug reactions, (2) medical error, (3) nosocomial infection, (4) malnutrition (see if you can find some medical journal references that discuss the reasons why so many hospitalized patients are dying from malnutrition), (5) outpatient care, (6) unnecessary procedures, and (7) surgery. The references given in this chapter will help. Also, if you type "death by medicine" into your Internet search engine, you will find some interesting Web sites on this subject. (b) How many deaths per year are attributed to alternative medicine? (The number is incredibly low.) The level of enhancement in benefit-to-cost ratio for electrotherapy, compared with conventional therapies, is highly dependent upon statistics like these. (c) Consider the 10,000 hospitals and 40,000 clinics (and other health care facilities) in the United States. If we assume that 50% of the iatrogenic disease related deaths occur in hospitals, and 50% occur in clinics and other health care facilities, on the average, how many deaths occur per year for each hospital and clinic-health care facility? Do these numbers seem believable? (d) What are the annual costs associated with these iatrogenic disease-related deaths?
2. The total power associated with the human body, at rest, is approximately 100W [51]. From the standpoint of various components and

organs of the body, the brain requires approximately 23W to operate, the heart (which has a 10% efficiency with respect to delivered power) requires approximately 13W, and the lungs require approximately 5W (the lungs require about 5% of our oxygen uptake to maintain activity). Assume the surface skin area for a 171-pound male is approximately 1.8 m^2. Also, assume this person has a 2-cm-diameter, 1-cm-deep, exposed skin tumor that is to be treated with an electrotherapeutic device. The tumor vascular structure is complex and poorly formed. A certain amount of liquid is released from the tumor area when treated with electrotherapy. Small-diameter Pt electrodes are applied that penetrate the tumor and peripheral normal tissue at a depth of 1 cm. (a) Knowing very little at this point, estimate the amount of electrical output power and direct current that an 8V electrotherapeutic device must deliver to treat the cancer. (b) Estimate the impedance of the tumor mass. (c) Estimate the current density at the outer periphery of the tumor if eight Pt wires are inserted around the tumor periphery. This current density should be fairly close to current densities associated with electrotherapeutic treatment of cancer tumors encountered in situ and in clinical practice, and to current densities that suppress proliferation of malignant cells in vitro (see Chapter 3).

3. When actual data is obtained, the output power and direct current are 27 times higher than the output power and direct current calculated in Exercise 2, and the apparent impedance is 27 times lower than one would expect for cancer tissue impedance. What could contribute to these discrepancies?
4. Repeat Exercises 2 and 3 for the 171-pound man's lung, assuming a lung tumor that is 2 cm in diameter. The lung area is estimated to be 800 cm^2. (Hint: depending upon the approach, the calculations might be quite similar to those obtained in Exercises 2 and 3.)
5. The estimates for the number of cells in our body vary, but it appears that we have from 3 or 4 trillion tissue cells, 35 trillion native cells, and up to 75 trillion total (tissue-native and foreign cells (such as bacteria); see [52]). We can make an estimate of 5 trillion tissue cells (5×10^{12}) in the 171-pound man. We will assume that each cell is rectangular, 20 μm on each side, and all cells are in intimate contact with their neighbors. We will simplify the electrical models for the basic metabolic rate and assume an ionic current density that is directed into one side of the cell and out of the other side of the cell. The current density for the individual cell's metabolic activity is approximately 1 mA/cm^2. The cell plasma membrane potential is 70 mV. (a) Estimate the power

requirements per cell. (b) Considering that 4.5% of the cells are involved with intense metabolic activity, calculate the total power for the human body while the body is at rest. Does the total power calculated agree closely with the power of the human body given in Exercise 2?

6. If we assume 2,500 Cal of food intake over a 24-hour period (all glucose), and if 100% of the glucose is converted to energy evenly among 5 trillion cells; then over that 24-hour period (86,400 seconds), that would amount to 0.029 Cal/sec. There are 4,186 J/Cal, and 1 J = 1 Wsec. Calculate the number of watts equivalent to an energy utilization of 0.029 Cal/sec? This number should be close to the total power given in Exercises 2 and 5.
7. Assume that a tissue is initially made up of healthy cells, each with a membrane voltage of 70 mV and a current density of approximately 1 mA/cm^2. Then the tissue becomes diseased. An electrotherapeutic device is applied to assist in the healing process. The electrotherapeutic device utilizes an average output voltage of 8V, where the output waveform consists of a low-frequency ac component with a dc offset. The offset may occur due to a charging effect, or it may be a waveform design feature. Assume you are applying this current to an area of approximately 7 cm^2. (a) What average current density would you expect to provide for the diseased cells that would avoid power levels and temperatures that could destroy the cells or burn the tissue? (b) Calculate the device average output current. After reviewing the figure caption for Figure 1.1, does this average current level seem reasonable and safe for visual disease applications? (c) Assume a 3.1-cm^2 circular conductive electrode is appropriately shaped and placed over a 3.1-cm^2 wound that is approximately 2 cm in diameter and 0.5 cm deep. A counter electrode surrounds the wound area and is in contact with normal tissue. Assume a current density of 1 mA/cm^2 and a total impedance (tissue, contact, and so forth.) of 1,000Ω. Calculate the treatment current and source voltage. Are these values reasonable with respect to the information given in Section 1.3?
8. Are there any potential temperature damage possibilities to tissue due to the average powers associated with typical electrotherapeutic device average output voltages and currents? Evaluate the resulting temperatures associated heat loss considering radiation only, heat loss by conduction, and heat loss by convection. Assume an electrotherapeutic application involving the treatment of a 2-cm-diameter tumor, with an applied voltage of 10V and a current of 50 mA.
9. In his book, *Nanomedicine*, Freitas provides interesting information concerning the number of specific atoms we have in our bodies [52].

He indicates that a 171-pound person, with a tissue volume of 0.037 m^3, has a total of approximately 7×10^{27} atoms in his or her body. (a) How did he get that number? Based on an assumption that the distance between atoms is 2.5Å and assuming that these atoms are arranged in a cubic lattice (a naïve assumption, but it often works for estimates), calculate the number of atoms in the body. (b) Calculate the number of atoms in a tissue cell that is 20 μm in diameter and cubic in shape (another naïve assumption). (c) Freitas gives the number of atoms for many of the elements in our bodies. Supposedly, out of that total, we have approximately 4.22×10^{27} atoms of hydrogen, 1.61×10^{27} atoms of oxygen, 8.03×10^{26} atoms of carbon, and 3.9×10^{25} atoms of nitrogen. Freitas continues into the heavier elements: 6.00×10^{18} atoms of mercury, 4.22×10^{18} atoms of arsenic, and 2.0×10^{17} atoms of uranium. What in heaven's name (that's a clue) are mercury, arsenic, and uranium doing in our bodies?

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2

Fundamentals of Electrotherapy

2.1 Answering the Basic Questions

After observing or experiencing the oftentimes beneficial results of electrotherapy, people's interest and curiosity take over and they ask a number of questions, including: "Why does the body respond to so many different forms of electrotherapy?" and "What is the scientific basis of electrotherapy?" Standard textbooks in anatomy, physiology, and immunology often do not provide satisfactory or complete answers to these questions. Although many factors need to be considered in order to address these questions, a relatively simple electrical model for human body healing and regulation processes can be developed using principles from wound healing, physics, chemistry, and biological sciences.

The early work of Galvani, Aldini, Matteucchi, and du Bois-Reymond concentrated on electrical conduction processes in nervous system tissue. Some of their results did include measurements of resting potentials (nontime varying, or dc potentials) and currents associated with wound sites. Resting potentials were reported by du Bois-Reymond in 1847, but he considered them to have only a minor part in the wound site response. However, the combined results reported by Galvani, Aldini, Matteucchi, and du Bois-Reymond demonstrated that biological tissues, in general, are electrically conductive. Their work indicated that a variety of electrical processes in the human body are important components of healing and regulation. Their results also served as an appropriate foundation for the development of Dr. Albert Szent-Györgyi's theories involving the semiconducting properties of proteins, lipid cell membranes, and DNA [1]. Szent-Györgyi proposed that sugars and phosphates in the DNA alpha helix support electron transfer and electron transport mechanisms.

Electrical conduction processes in DNA molecules have been investigated to the point that DNA strands have been proposed as basic structures for quantum wires and mesoscopic electronic devices [2]. Electron tunneling in proteins has been reported [3], and electron transfer chemistry appears to serve as a trigger for protein folding events [4]. The similarities in characteristics between modern microelectronic materials and biological materials, along with similarities in biological structures and microelectronic circuits, appear to be providing a framework for a new understanding of biological systems [5].

Wound healing research has clearly demonstrated that many elements of healing and regulation involve electrical and electrochemical processes. The human body has its own endogenous electrotherapeutic capabilities. The human body responds to electrotherapy because biological systems are electrical and electrochemical with respect to both form and function. The human body possesses a set of integrated electrical and electrochemical systems, which are involved in regulation and healing. The theory and principles behind these processes have been studied for more than 200 years.

2.2 Simple Bioelectric System Models Based on Wound Healing

By combining our current knowledge of basic biology, chemistry, and physics with some of the results obtained in wound healing research, a set of simple bioelectric system models can be structured and used to describe and analyze some of the characteristics associated with physiological response mechanisms in healing and regulation. Also, these relatively simple models provide the type of information that can be useful in the electrotherapeutic device design process.

We might consider two different types of wounds: a laceration and an ulcer. A laceration and an ulcer can have significantly different models and mechanisms that characterize the bioelectric events in their respective wound healing processes. But they do have a few things in common.

With respect to a laceration type injury, the injury site currents and voltages reported by Galvani, Aldini, Matteucci, and du Bois-Reymond in the 1700s and 1800s could be incorporated into a simple electric circuit model shown in Figure 2.1. Using this very simple equivalent circuit for an injured tissue-body fluid structure, injury site potentials of 20 to 40 mV and a total resistance of 2,000Ω, would produce injury currents of approximately 10 to 20 μA. These currents would be reasonably close to measured values. One might ask, however, "What is the mechanism that produces the injury site voltage. What are the characteristics of the conductive pathway that produce the injury currents? Why is the injured region electrically positive with respect to the adjacent uninjured tissue?"

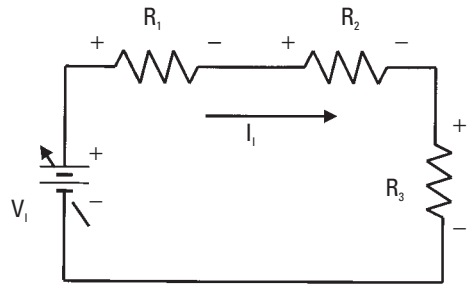


Figure 2.1 Equivalent electrical circuit model for a wound site. The injury potential, V_I, and injury current, I_I, associated with the wound are shown along with three resistors representing the resistances of different tissue layers. As the tissue heals, V_I and I_I decrease.

The tissue-injury site bioelectric model is not quite as simple as Figure 2.1 seems to imply, and the relationship between skin layer geometry and polarity of the equivalent skin battery is not clearly defined or shown in Figure 2.1.

Fowles and Edelberg [6, 7] describe electrodermal systems with individual endogenous voltages at each tissue layer (Figure 2.2). According to their models, under normal conditions, the surface of the skin possesses a negative potential with respect to the underlying layers. Under normal conditions (no injury), the combination of the movement of water and movement of ions maintains equilibrium and regulates the endogenous potentials associated with each tissue layer.

In the models derived from the work of Fowles and Edelberg, the type of current and conductive processes associated with the currents designated as I_D, I_{EP}, and I_C (shown in Figure 2.2) must be addressed. This model will generate more questions, such as: Are these currents essentially determined by the transport of ions? Is there a contribution based on the transport of electrons? Are these currents essentially drift currents, or is there evidence of diffusion processes [8]? Are these direct currents, or is there a time-varying component?

The type of current and the type of mobile charged entity being transported can determine the influence that endogenous and exogenous electrical stimulants, and their associated electrochemical effects, can have on biological systems. The type of current and mobile charge entities involved will have significant impacts on bioelectric processes involved in healing, metabolism, and growth. The characteristics associated with these currents and mobile charges, combined with other information, will help to determine appropriate current and current density magnitudes, polarities, frequencies, waveforms, and treatment duration in the design of electrotherapeutic devices and treatment protocols.

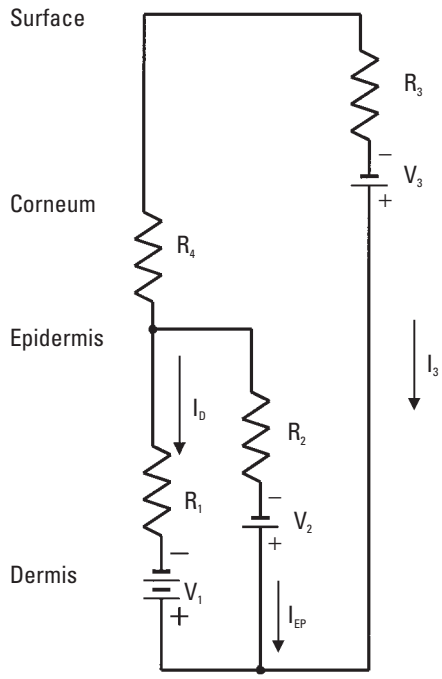


Figure 2.2 Equivalent circuit for different layers of skin, representing the first three layers of tissue (based on the work of Fowles and Edelberg [6, 7]). Resistors R_1, R_2, and R_3 represent combinations of sweat duct and sweat duct wall resistance. R_4 represents the corneum resistance.

Although the bioelectric model of Figure 2.2 is somewhat qualitative, Fowles and Edelberg designate the potentials V_1 and V_2 as trans-sweat duct potentials (in the dermis and epidermis, respectively) that occur as a result of differences in ion permeability and differences in ion concentration across sweat ducts. The potential V_3 represents a liquid junction potential in the corneum. The conductive pathways (represented by the various resistance values) consist of tissue and fluid. These potentials, conductive mediums, and conductive pathways contribute to a skin potential (V_{SP}), which can be measured.

The Nernst equation can be utilized to estimate a value for a basal skin potential (V_{BSP}) if Ag/AgCl-measuring electrodes are used and a potassium ion (K^+) gradient is considered [9]:

$$V_{BSP} \approx (2.303)(RT/zF)\log_{10}\left[\mathrm{K}^+\text{conc. elect. electrolyte}\right]/\left[\mathrm{K}^+\text{conc. tissue}\right]\text{mV} \tag{2.1}$$

where R is the gas constant (8.314 J/°K – mole), T is temperature in °K (20°C = 293.16°K), z is the valence of the ion (1 for K^+ ion), and F is the Faraday constant (96,487°C/mole). In this case, $RT/zF \approx 58$ mV. Using a 0.5% KCl electrolyte and achieving a 2:1 K^+ ion concentration ratio between the electrode electrolyte and the tissue, a basal skin potential of 17.45 mV would be expected. This is a measured voltage.

However, the V_{BSP} surface measurement might be considered incomplete or misleading with respect to actual internal skin battery voltages in electrodermal models. Considering only one ionic species (K^+), an external electrode touching the surface of the skin and the Nernst equation, this combination may not give an accurate indicator of the potentials associated with multiple skin layers and multiple ions. The Goldman equation might provide an upper limit for a resting skin potential (V_{RSP}) based on a cell membrane resting potential (V_m) in tissue [10]:

$$V_{RSP} \approx V_m = (58)\log_{10}\frac{P_K\left[\mathrm{K}^+\right]_O + P_{Na}\left[\mathrm{Na}^+\right]_O + P_{Cl}\left[\mathrm{Cl}^-\right]_i}{P_K\left[\mathrm{K}^+\right]_i + P_{Na}\left[\mathrm{Na}^+\right]_i + P_{Cl}\left[\mathrm{Cl}^-\right]_O}\,\mathrm{mV} \qquad (2.2)$$

The various P factors represent membrane relative permeabilities for each ion, the terms in brackets represent ion concentration outside ($[\ ]_O$) and inside ($[\ ]_i$) the cell membrane. Estimating permeabilities and using information from Watson [10],

$$V_{RSP} \approx (58)\log_{10}\frac{(1.0)[200]_O + (0.04)[440]_O + (0.45)[50]_i}{(1.0)[400]_i + (0.04)[140]_i + (0.45)[560]_O}\,\mathrm{mV} = -83.4\ \mathrm{mV}$$

Under the influence of the various potentials, the movement of ions (K^+, Na^+, Cl^-, and so on) contributes to the associated current in the tissue medium, and ion flow is considered to be the dominant component of current in this electrodermal model. Although (2.1) and (2.2) have somewhat different origins, they both provide equations that are useful in comparing skin potential measurement data with actual skin battery and epidermal battery voltages.

At this point, we have been able to calculate skin voltages that are quite close to voltages measured for injured and uninjured tissue. Using Ohm's law (current, I, equals voltage, V, divided by resistance, R), voltages in this range applied to tissue resistance values in the kilohm range, will produce the microamp current levels that have been measured at injury sites. Therefore, in order to be therapeutically efficacious, electrotherapy devices should deliver current intensity levels that are reasonably close (within an order of magnitude) to the injury current values. Once current intensity requirements have been

determined from the standpoints of therapeutic efficacy and safety, the injury site polarity issue needs to be addressed.

Figure 2.3 shows what happens when the tissue structure and its equivalent electrical circuit are disturbed or lacerated [11]. The lower level of the laceration (or the region near the center of the laceration) has a positive polarity compared with the surface tissue. Therefore, the center of the injury site is positive with respect to the normal surrounding surface tissue. With this injury, the V_3 pathway is opened and V_1 is shorted, leaving a conductive pathway with a resistance R_T. The epidermal sweat duct potential, V_2, is exposed to a conductive pathway, R_{EQ}, along the exposed tissue allowing ionic current to flow through the subdermal region [11, 12]. In this configuration, the positive polarity associated with the center of the injury site is produced by a disturbance, or laceration, of the tissue structure. This produces a positive skin potential polarity at the center of the injury, as shown in Figure 2.3. Chakkalakal, Wilson, and Connolly [11] report measured values of canine injury site voltages of 23 to 47 μV and currents of 2.4 to 28 μA.

As the tissue layers heal, from bottom to top, the injury site positive potential decreases to the point of becoming negative when the tissue structure is restored and the healing process is complete. The endogenous positive injury potential can contribute to the healing process by promoting the movement of

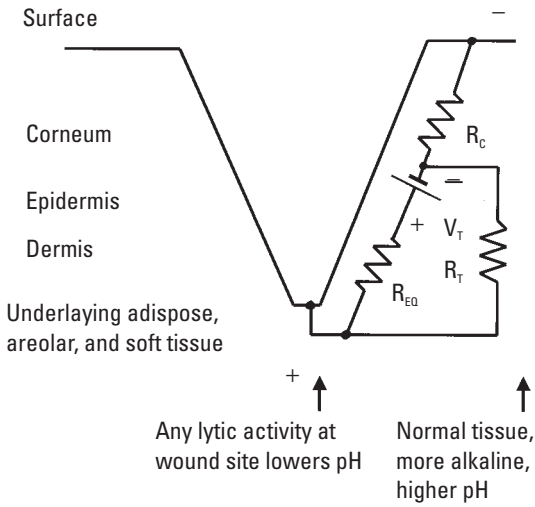


Figure 2.3 Positive injury potential due to polarity of the equivalent transcutaneous potential (V_T) at the injury site. In this figure, the parallel voltage sources of Figure 2.2 are combined into an equivalent series circuit. R_C represents the resistance of the corneum, R_T represents the combined resistance of the various tissue layers, and R_{EQ} represents the equivalent resistance for the combination of R_1, R_2, and R_3. (*After:* [11, 13, 14].)

charged entities (electrons, protons, certain enzymes, white blood cells, and so on), which can enhance metabolic processes, cell-tissue proliferation, and immune system response. The tissue at the injury site becomes more alkaline (normal) as it heals.

From an electrotherapeutic standpoint, an exogenous source of current, at the appropriate magnitude, could further enhance the healing process. Therefore, the design of therapeutically efficacious and consistent electrotherapeutic devices will require output capabilities that can (1) provide specific current intensities in the microamp or low milliamp range, (2) utilize relatively low frequencies that are compatible with ion flow velocities, molecular transport, and electro-osmotic mechanisms, and (3) incorporate specific waveforms that can achieve optimum effects for different therapeutic applications.

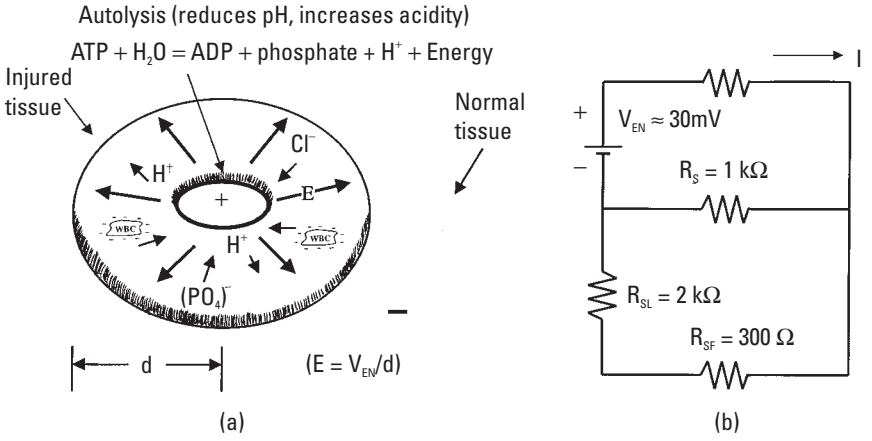
If an ulcer is being considered as the wound site or injury site, some fundamental differences must be recognized between an ulcer wound and a laceration wound, and these differences must be incorporated into the equivalent electrical circuit and mathematical models. In this case, we can consider the ulcer to be a necrotic-acidic wound site similar to the necrotic mass that Nordenström uses in his theories concerning the treatment and remission of malignant and nonmalignant tumors [13, 14].

At or near the center of the ulcer, diseased or damaged cells are being destroyed by cellular lytic activity. As the cells undergo lysis (chemical destruction of the cell), acidic byproducts of the lytic activity accumulate in the diseased or injured region. As shown in Figure 2.4(a), the pH (acidity) in the center of the diseased or injured region is much lower than the pH of the normal surrounding tissue (normally, more alkaline). With a degraded fluid/tissue matrix at the center possessing a low pH, and healthy surrounding alkaline tissue, we have the basic building blocks for a wet cell battery.

The endogenous voltages associated with injury, inflammation, or ulceration have been measured, and they are often in the range of 2 to 40 mV, with associated currents of 0.1 to 30 μA and current densities of 0.5 to 25 $\mu A/cm^2$ [11, 13, 15]. The equivalent electrical circuit for this wound or injury site, and associated electrical activity, is shown in Figure 2.4(b).

Knowing the injury potential, an electric field, E (in volts per meter), as shown in Figure 2.4(a), can be obtained by dividing the endogenous injury voltage, V_{EN}, by the distance between the center of the injury site and the normal tissue, d. The concept of an electric field involves field intensity lines that originate from a region of positive polarity and terminate in a region of negative polarity. The presence of an electric field at the injury site has significant consequences with respect to metabolism, energetic processes, and immune response.

$$E = V_{EN} / d \tag{2.3}$$



V_{EN} = Endogenous skin battery (electric field, E, produced by voltage over distance)
R_{DA} = Dermal, adipose and areolar tissue resistance
R_{SL} = Surface layer resistance
R_{SF} = Surface body fluid resistance
R_S = Soft tissue resistance

Figure 2.4 (a) Wet cell battery and tissue conductive path model for a wound or injury site. As long as the injury exists, catabolic reactions will promote polarizing reactions at the injury site. This will lower the pH at the injury site, produce voltages and electric fields between the diseased or damaged tissue and the normal tissue, and promote the transport ions such as H^+, $(PO_4)^-$, and Cl^-. Also, white blood cells (WBC), which have a negative surface charge, will be attracted to the positively charged center of the injury or disease site to accomplish their immunologically important tasks. (b) The equivalent electric circuit for this system is shown with a relatively static (dc), endogenous epidermal battery source and a number of resistances associated with the conductive pathway in the tissue-fluid system. The current in this system involves mobile ions. (*After:* [11, 13, 14].)

Charge is often designated as Q for total charge, and q or e for charge on a particle, where $|q|$ or $|e| = 1.6 \times 10^{-19}$ C. Coulomb's law indicates that any charged entity located in this electric field will be under the influence of a force, F, that is the product of the electric field and the charge. Newton's second law of motion states that this force will produce motion, and the charged entity (with mass m) will move with a velocity $v(t)$. The velocity will increase with time (acceleration, a) as long as the charged entity can move with minimal interference:

$$F = \mathrm{E}q = ma = m\left(dv(t)/dt\right) \tag{2.4}$$

These two equations and the microscopic form of Ohm's law are all that one needs to develop simple bioelectric relationships and models that help explain how electrotherapy can contribute to the transport and synthesis of biologically important molecules that support wound healing processes.

If the center of a wound (laceration, ulcer, and so on) has a lower pH than the surrounding tissue (due, in part, to lytic activity), there will be an excess of positively charged hydrogen ions at the center. The positively charged hydrogen ions are free to move away from the low pH region toward the more negatively charged alkaline region, where the uninjured or normal tissue is located, as shown in Figure 2.4(a). As positively charged hydrogen ions (protons) are transported from one location to another in an electrically conductive biological system pathway, they can interact with tissue and cells that need repair. The movement of these protons can influence the proton concentrations and proton gradients associated with mitochondria located in the cytoplasm of various cells. Many cell models do not allow the passage of current from the interstitial space through the cytoplasm. However, a significant amount of recent research on cell membrane ion channels, bio-impedance, and phosphorylated nucleotides provides strong evidence that ionic currents (direct and alternating) can flow through cells.

Results at the molecular, cellular, and tissue levels provide support for ionic current flow (including proton transport) across cell membranes. Cheng et al. studied the effects of relatively low-level direct electric currents (dc) on ATP production in murine tissue [16]. Adenosine triphosphate (ATP) production, amino acid transport, and protein synthesis increased significantly for total direct currents in the range of 6 to 500 μA, involving tissue immersed in buffer medium. Most of the current flow was in the buffer medium. For total direct electric current levels within this range, Cheng and his colleagues observed increases in ATP production up to 500% [16].

Proton pumping across a cell's inner mitochondrial membrane promotes production of the phosphorylated nucleotide, ATP. ATP and other phosphorylated nucleotides provide the energy currency for biological systems. These molecules are vitally important for many biological processes including muscle activity, vision, cellular metabolism, immune response, digestion, reproduction, gene expression, and nervous system activation.

The transport of free electrons, also influenced by the injury site potential, can have an effect on the production of phosphorylated nucleotides in cells. The movement of free electrons can influence shuttle electron transfer and oxidation-reduction mechanisms in the mitochondrial respiratory chain, which would have an effect on ATP production.

Huang et al. observed variations (approximately 30%) in astrocyte energy metabolism (aerobic glycolysis) with the application of low-level static (dc) electric fields in the range of 1.5 to 15 V/cm [17]. Also, electrical stimulation appears to activate or accelerate gene expression [18, 19].

Again, the question arises: For a wound or injury site, what is the physical, chemical, and/or mathematical basis for endogenous voltages, such as V_{EN} of Figure 2.4? With lytic activity and a central region of low pH, the center of the wound or injury appears to have an abundance of ions including hydrogen, phosphates, chlorides, and hydroxides. To address this question, another version of the Nernst equation can provide a means to estimate the endogenous injury potential, V_{EN}, based on pH differences between the ulcerated and normal tissue. The pH differences will determine the potential difference (voltage) between the two regions. For instance, if we assume the pH of the injury site is equal to 3.0 (highly acidic) and the pH of the normal tissue, or reference tissue, is 6.0, there is a difference of –3 pH units between the injured tissue and normal tissue. Focusing on pH only, the equation for the Nernst potential, V_N, can be simplified as follows:

$$V_{EN} \approx V_N \approx V_O - 2.303\left(RT/zF\right)\left(\Delta pH\right) \tag{2.5}$$

A plot of V_N versus pH will yield a straight line with a slope that is equal to approximately 58 mV/pH unit change at 20°C [see the relationship between (2.1) and (2.5)]. If a reference potential of 0V is established at a pH of 7 (neutral), a difference of 3 pH units between the injured tissue and reference tissue would result in a V_N of approximately 174 mV. Generally, the injury site potential differences are one-third of this value. However, to provide protection from bacterial infection, normal skin pH is generally a little more acidic and is lower than the assumed pH of 6.3. So, the value for V_{EN} between the acidic injury site and the slightly acidic reference tissue would most likely be less than 174 mV. Also, as the wound site model of Figure 2.4 indicates, negatively charged mobile ions can have a substantial effect on V_{EN}. In addition, for a number of reasons, some of the injury site voltage could be dropped across the electrode-tissue interfaces when the injury potential is being measured.

Another question that might be asked for both the wound or injury healing model, involving lacerations and ulcers, is: What is the physical, chemical, and/or mathematical basis for the currents that are associated with the wound or injury site potential, and what is producing these currents? Considering a wound site involving a laceration or ulcer, the current associated with the region between the injured and normal tissue would be due (in part) to the flow of ions that are under the influence of the wound site electric field, E, produced by V_{EN}. One approach might be to employ the same type of equations that are used to calculate electrical current, *I*, and current density, *J*, associated with metals and semiconductors, and assume that the flow of ions occurs in a soft tissue matrix of cells and body fluids that has electrical properties similar to those of a saline solution:

$$J = I/A = \sigma \mathrm{E} = pq\mu \mathrm{E} = pev_D \tag{2.6}$$

Assuming a hydrogen ion mobility, μ, of 5.7×10^{-3} cm^2/V sec (close to μ for a saline solution), a density, p, of hydrogen ions of 6×10^{16} / cm^3 (pH = 4), a cross-sectional area, A, at the wound site of approximately 1 cm^2, and an endogenous wound site electric field of approximately 42 mV/cm, the current density would be approximately 2.3 μA/cm^2, the current would be approximately 2.3 μA, and the average drift velocity, v_D, for the hydrogen ions would be approximately 0.0024 mm/sec. This calculated value of drift velocity may appear to be very low. For processes involving electrolysis at higher current and voltage levels, at a pH of 3, Berendson and Simonsson [20] provide data indicating average drift velocities for hydrogen ions of approximately 0.0004 mm/sec. This is a much lower drift velocity than the previously calculated value. In fact, the average drift velocities for heavier ions would tend to be even lower. This is an important factor that will be discussed in more detail in Chapter 3. The calculated values of current, and current density, are within the range of values reported. The measured current density and current values are often higher than those calculated in this example, because there are other positive and negative ions being transported under the influence of the injury site electric field, along with a variety of larger charged molecules.

Referring to (2.4), the force on an electron or ion, with a charge of 1.6×10^{-19} C, located in an electric field associated with a 30-mV injury potential and a distance of 0.1 cm, is 4.8×10^{-18} N. Forces required to break chemical bonds must be more than 2 million times stronger than the force calculated for these conditions. However, combining the appropriate conductivity data with Ohm's law, it is clear that voltages of this magnitude can induce biologically significant currents in a conductive medium (such as tissue or body fluid).

Nordenström has shown that electro-osmosis (the movement of water under the influence of an electric field) can occur at surprisingly low voltages and electric field intensities [13]. The movement of ions and water, over a period of time, can have significant effects on chemical bonds and cellular viability. A specific voltage or electric field intensity may yield calculated forces and energies that appear to be much too low to have a direct effect on the breaking of a chemical bond, or to have a biological impact. However, that one result does not necessarily mean that a very low electric field does not have an effect on bonds or biological material structure. Figure 2.5 shows the effects that relatively low current densities and low-level electric fields can have on cells and tissue. Even at low levels of current and voltage, cells and tissues that are electrically stimulated show gradual changes in structure or morphology. Electrically induced structural variations in cells and tissues can produce or promote changes in function that can have significant value in wound healing processes.

Equation (2.6) describes a fundamental charge transport electrotherapeutic process that promotes or controls healing, metabolism, immune function, gene

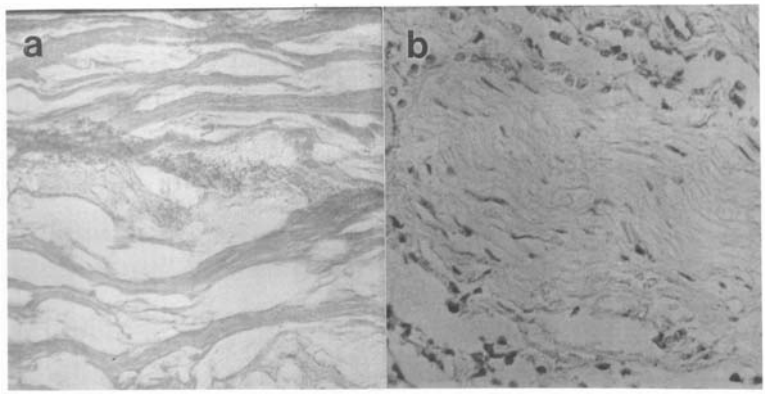


Figure 2.5 Histologic specimens of (a) collagenous cathodic tissue region and (b) anodic fibrous tissue region. Initially, both tissue regions possessed the same morphology. A negatively biased electrode (cathode) is placed in the region of (a), and a positively biased electrode (anode) is placed in the region of (b). As electric current starts to flow in the tissue, the tissue morphology begins to change, producing cathodic collagen material and anodic elastic fibrous material. These histologic specimens indicate that the application of electric current to tissue can change tissue structure resulting in a possible influence on organ function. (Courtesy of Björn E. W. Nordenström, M.D., Ph.D., professor emeritus in Radiology, Karolinska Institute, Stockholm, Sweden.)

expression, and nervous system activation This equation has applications in electric field assisted transport of charged entities (electrons, protons, large molecules, amino acids, proteins, cells, and so on). Also, for electro-osmosis, an electric field associated with an injury site or tumor can contribute to the movement of water through a number of mechanisms involving fixed or moving charges.

Some basic principles of biochemistry and physiology, combined with (2.5) and (2.6), indicate that many important biological system processes and functions (including metabolism, genetic regulation, immune function, hormonal balance, renal function, cardiovascular condition, healing, growth and development, and so on) can be influenced by endogenous injury or disease site potentials through a variety of ion/molecule transport mechanisms. These endogenous injury or disease site potentials can have a significant influence on biological structure and function, because they have the ability to assist in transporting ions and molecules to locations where they are needed.

Many processes in the human body depend upon electrical or electrochemical mechanisms. Electrotherapeutic techniques complement what the biological system is already doing. The application of external or exogenous

voltages, electric fields and currents can be beneficial in many cases where the biological system's natural healing and regulatory processes require some assistance. This kind of outside assistance, using appropriate and effective protocols, is the essence of electrotherapy. In this case, electrotherapy is used as a complementary or adjunct modality to augment the human body's normal electrochemical and electrical processes in healing, regulation and development. Also, electrotherapy offers significant advantages over many conventional therapeutic modalities when one considers the combination of effectiveness, absence of harmful side-effects, low cost, safety, reliability, reproducibility, ease of application, and compatibility with other therapeutic techniques.

2.3 Electrotherapeutic Device Design Implications

Equations (2.5) and (2.6) can be applied to specific electron/ion/molecule transport processes that influence biological structure and function. Even the simplest wound healing models, combined with mathematical relationships like (2.5) and (2.6), can indicate appropriate design parameter values for electrotherapeutic devices that are able to complement natural endogenous bioelectric processes in the human body. By using a simple set of mathematical expressions—including those derived from Coulomb's law, Newton's second law, and Ohm's law, along with several forms of the Nernst equation—information and concepts concerning the effects of electric fields and electric currents on biological systems and processes can be visualized and described. Some of these have been previously discussed in Section 2.2.

For electrotherapeutic healing protocols not associated with the treatment of tumors, the combination of wound healing models and their electrical circuit equivalents (as shown in Figures 2.1, 2.2, and 2.3) often indicate that the best design choice for electrotherapeutic device current levels would appear to be in the microamp range. Most of the successful applications of electrotherapy to wound healing, destruction of pathogens, and treatment of visual disease have been accomplished with direct electric currents in the microamp to low milliamp range. Merriman et al. provide results that show significant inhibition of bacterial growth (*Staphylococcus aureus*) using direct currents at 500 μA to 1 mA over time periods of 1 hour to 3 days [21]. They indicate that their bacterial inhibitory effect results obtained at 500 μA, over periods of 1 hour, appear to coincide with several clinical studies showing increased ulcer healing rates with the use of direct currents at these same microamp levels [21].

In vitro results for ATP production, amino acid transport, protein synthesis, and dry tissue damage reported by Cheng et al. [16] indicate that for small areas, average therapeutic current levels less than 200 μA would be preferred for certain electrotherapy applications. From the standpoints of patient comfort

and safety and the minimization of possible peripheral tissue damage, average therapeutic current levels less than 150 μA appear to be more prudent for very sensitive regions (such as the visual system). Appropriate therapeutic current levels should be determined by the tissue and specific region of the body being treated. For dry tissue, Cheng et al. reported that some tissue destruction occurred at current levels higher than 50 μA.

High current levels should be evaluated carefully before being considered in electrotherapy applications. A 200-μA exogenous current level is significantly larger than many of the naturally occurring average endogenous healing current levels that have been measured for humans. Average exogenous current levels of 200 μA, or higher, would be reasonable for treating many large-area connective tissue injuries, lacerations, wounds, and tumors. Average current levels in many large-area wound healing applications range from 30 to 1,000 μA [22]. However, for electrotherapy applications in visual disease (macular degeneration, retinitis pigmentosa, diabetic retinopathy), a 200-μA exogenous average current level, applied to a closed eyelid, could be very uncomfortable. In the case of visual disease, therapeutic efficacy and patient comfort considerations would constrain average treatment current levels toward the range of 50 to 150 μA. Initial studies, along with the results achieved in various clinical trials in the electrotherapeutic treatment of retinitis pigmentosa and macular degeneration, provide support for the 50- to 150-μA average treatment current range for visual disease applications [23, 24].

With respect to waveform and frequency, the research literature concerning electrotherapeutic effects on cells and tissues indicates that rectangular waveforms at frequencies in the range of 0 to 150 Hz are very effective in healing vascular damage and promoting cell proliferation. Electric currents and electric fields with frequencies of 72 and 105 Hz can promote capillary healing. Electric currents and electric fields at frequencies close to 10 Hz can promote DNA replication, cell proliferation, lymphatic drainage, blood pressure reduction, and wound healing [25–27].

Additional areas that need to be considered involve questions concerning the dominant type of charged carriers, at specific injury sites, that are associated with endogenous or naturally occurring current levels. If the bioelectric effects at the injury site are dominated by the transport of heavy ions, such as large charged molecules, and water, this would tend to influence the design choices involving electrotherapeutic device output frequencies. The transport of large molecules, the transport of ions with large hydration spheres, and water transport mechanisms could be more responsive at lower frequencies. In electrotherapy, this is sometimes the case when the health problem involves edema. A number of electrotherapeutic device protocols recommend a frequency of 10 Hz (at 100 to 300 μA for 5 minutes) to promote lymphatic drainage or treat edema.

At this point it is clear that some simple wound healing concepts and circuit equivalents, combined with a few basic equations, can provide a significant amount of useful qualitative and quantitative information. This information can be very helpful in the establishment of design concepts and the choice of an initial design approach for a variety of electrotherapeutic devices and treatment protocols.

2.4 Summary

The early work of Galvani, Aldini, Matteucchi, and du Bois-Reymond, during the eighteenth and nineteenth centuries, provided some of the first evidence that electrical and electrochemical processes were associated with healing and regulation in biological systems. The unique ideas presented by Szent Györgyi indicated that the electrical characteristics of living systems extended right down to electron transport mechanisms at the molecular level. The types of tissue models developed by Fowles and Edelberg helped to define the electrical properties and characteristics of normal and injured tissue. These results, and the work of many others, assisted Nordenström and Becker in their efforts to describe the structure and function of the human body as it is influenced by the combination of electrical, chemical, and electrochemical processes.

One has to keep in mind that the theories and models proposed by these people are not based on supposition and wild guesses. Their theories are based on the application of the fundamentals of physics and chemistry, accurate measurements, rational thinking, and the scientific method. What is interesting about the ideas and theories these people have developed, is that we can start out using some very well established and very basic tools of physics and chemistry (i.e., Coulomb's law, Faraday's law, Gauss's law, Ohm's law, Maxwell's equations, Newton's second law, transport equations, electrochemical reaction equations, Nernst equation, Goldman equation, free energy equations, energy transfer relationships, and so on). From these fundamental relationships, we can calculate the various electrical and electrochemical parameters and characteristics associated with living systems. And in general, the electrical and electrochemical parameters and characteristics we obtain, using fundamental relationships in physics and chemistry, are in close agreement with ideas, theories, measurements, and models presented by Szent-Györgyi, Fowles and Edelberg, Nordenström, and Becker. Careful measurements, photographic evidence, and clinical results verify that the ideas, theories, and models presented by these individuals are valid, consistent with scientific principles and are applicable to a variety of therapeutic techniques.

With respect to medical practice and therapeutic options, we still appear to be living under the same type of inquisitional dogma, arrogance, and

constraints that were imposed on William Harvey in the seventeenth century. And some of us will continue to be subject to the same type of violence that Harvey faced when we stray from the medical status quo. The seventeenth century playwright Moliére is quoted as saying, "Nearly all men die of their medicines, not of their diseases." In some cases, that statement is as true today as it was more than 350 years ago. The medical profession needs to be sufficiently concerned and motivated to incorporate into practice the ideas, theories, and methods promoted by the likes of Nordenström, Becker, and other highly principled and dedicated medical doctors. If this is accomplished, patients will be healthier and they will live longer. If this is not accomplished, Moliére's quote will continue to rule. If this book does nothing else, I hope that it gets that idea across to the reader.

Exercises

1. Current (I) is defined as a change of charge (Q) with respect to change in time, where $I = dQ/dt$. Current density (J) is current divided by area (A), where $J = I/A$. Charge (Q) is a function of charge density (ρ_{CH}) and volume, where $Q = \rho_{CH}$ (volume). Mobility (μ) is the ratio of the drift velocity (v_D) to the electric field intensity (E), where $\mu = v_D/\mathrm{E}$. Derive the last expression shown in (2.6) from the information shown in the first two sentences of this exercise. Then, derive the previous two expressions shown in (2.6).
2. Using a simple ballistics model, see if you can develop a set of relationships that make the progression from an electron that accelerates under the influence of an electric field, suffers a collision and stops, starts moving again, and repeats the process (where electron velocity, as a function of time, exhibits a continuous saw-tooth waveform shape). Develop a set of relationships that make the progression from the ballistic model for conduction electrons to Ohm's law.
3. From the standpoints of molecular bonding and energetics, is there enough energy associated with the wound site electrical parameters to have an impact on chemical bonds, metabolism, cell interactions and structure and function in tissue? An expression for the standard free energy ($G^{O'}$, pH = 7) is as follows: $G^{O'} = -nfV^{O'}$, where n represents the number of electrons transferred per mole, f is Faraday's constant in kcal/V (23 kcal/V), and $V^{O'}$ represents the net standard oxidation-reduction potential in volts. In order to synthesize ATP, an energy of −10 to −14 kcal/mol is required. If $n = 2$, a minimum potential of approximately 0.218V would be necessary to produce enough energy

to synthesize ATP and many other biologically important molecules. The potentials that would be present at each cell site, produced by endogenous injury potentials in the range of 17 to 60 mV, would be miniscule. The tiny voltages present at each cell site could not provide enough energy to influence the synthesis of ATP or any molecule. So, how can a small exogenously applied voltage enhance the production of biologically important molecules, if the healing mechanisms and the electro- therapeutic mechanisms fail to meet energy requirements for the necessary chemical reactions?

4. If the pH increases or decreases, how does this effect electrotherapy?
5. In the process of electro-osmosis, explain at least one mechanism by which a positively charged ion, under the influence of an electric field, can move water molecules away from a positively charged region.
6. The photon energy of an electromagnetic wave (i.e., radio wave, microwave, millimeter wave, infrared, visible light, ultraviolet, and X-ray) is given as Planck's constant ($h = 6.6 \times 10^{-34}$ J sec, or 4.1×10^{-15} eV sec) times frequency (f), where $E = hf$. Assume that the electromagnetic wave is a 1-GHz (1 billion Hz) radio wave. The photon energy for the radio wave is much too small to have an effect on molecular bonds. But we know from experience that radio waves at even lower frequencies have significant effects on biological systems. With this in mind, how can a 1-GHz electromagnetic wave have an effect on biological systems and molecules? What kinds of photon energies are high enough to have a direct impact on molecular bonds? What is the therapeutic relevance here?
7. What other aspects of skin architecture might we consider for the process of wound healing?

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3

Electrical Properties and Response Characteristics of Cells, Tissues, and Organs

3.1 Electrical Properties of Cells

Animal and plant cells consist of many materials and molecular structures that are electrically conductive or electrically responsive. Some of the primary cell molecular components (i.e., nucleic acids and proteins) exhibit semiconducting properties. As shown in Figure 3.1, the plasma membrane surface has a number of molecular structures (i.e., glycoproteins) that are negatively charged and contribute to the net negative surface charge density associated with plasma membranes of most cells. Asymmetrical disturbances of the cells surface charge density can have an effect on the response of certain plasma membrane structures such as ion channels and receptors. As Figure 3.1 indicates, the cytoplasmic fluids inside biological cells and the surrounding medium have appreciable ionic conductivity. The cytoplasm is described as a liquid or gel-like substance that can apparently move or *stream*; that is, it can make the transition between a gel and a liquid state and it can exhibit phase transitions (often involving large volume changes) with certain mechanical, thermal, electrical, or chemical stimuli. For our initial analytical and modeling efforts, let us assume the cell's cytoplasm is in the liquid state.

Electron transport, transfer, and exchange mechanisms have been associated with many cellular components and functions such as immunoreceptor recognition and signaling, ligand-cell receptor binding, cellular respiration (mitochondria), and photosynthesis (chloroplasts). The nervous system and

cardiovascular system have significant electrical and electrochemical activity associated with specific cell types and tissue structures.

Figure 3.1(a) shows a simplified structural overview of a eukaryotic cell membrane, and regions or components of the cell that have electrical properties or exhibit electrical responses. The rather close-packed molecular structures inside the cell (cytoskeleton, nucleus, organelles, and membrane protein structural elements) located within the cytoplasmic space are not shown. In Figure 3.1(b), an electrotherapeutic current flows and a charge accumulates on the surface of the hormone receptor. The accumulated charge could activate the same series of chemical events that are normally associated with the binding of the hormone to the receptor. Now, the electrotherapeutic signal can influence regulation and healing processes and compensate for deficiencies in body chemistry, or complement on-going chemical processes in cellular activity.

The influence of exogenous electrical currents and electric fields, and their involvement with various cell plasma membrane receptors, has been well documented. References [1–7] provide a very small sample of the data and results that indicate the involvement or direct interaction between exogenous electrical currents and electric fields, and cell plasma membrane receptors. These results indicate the participation of a wide variety of receptors that influence Ca^{++}, inositol – phospholipid and cyclic AMP signaling pathways. The type of receptors involved includes receptor-operated ion channels, β-adrenergic receptors, neuronal receptors, N-methyl-D-aspartate receptors, and VEGF receptors in vascular endothelial cells. Khatib et al. [6] discuss the net electrical charge and electrically induced redistribution and movement of transferrin receptors, epidermal growth factor receptors, and low-density lipoprotein receptors. They indicate that these movements could induce signaling cascades in cells. There is strong evidence that exogenous electrical currents and applied electric fields influence cell receptors and the cell signaling pathways that they activate. Figure 3.1(b) provides a diagram for one of the proposed interaction mechanisms involving a cell membrane receptor and accumulated electrical charge interaction as implied by Khatib et al. [6].

Electric fields exist in and around many multicellular organisms and isolated cells. Some cellular electric fields can be the result of polarization effects from ion channel and ion pump activity in the cell's plasma membrane [7]. Also, isolated cells in fluid can exhibit properties similar to colloidal particles in suspension. The cell's plasma membrane surface charge density can attract a positively charged ionic cloud, producing a zeta potential. The zeta potential is often defined as the potential associated with the ion layers at the surface and near-surface of a cell, electrode, or colloidal particulate, immersed in or suspended in fluid. If the zeta potential is reduced (which can happen if the pH of the surrounding fluid medium decreases), cellular particles will aggregate [8], which can interfere with the normal flow of body fluids. For immunological

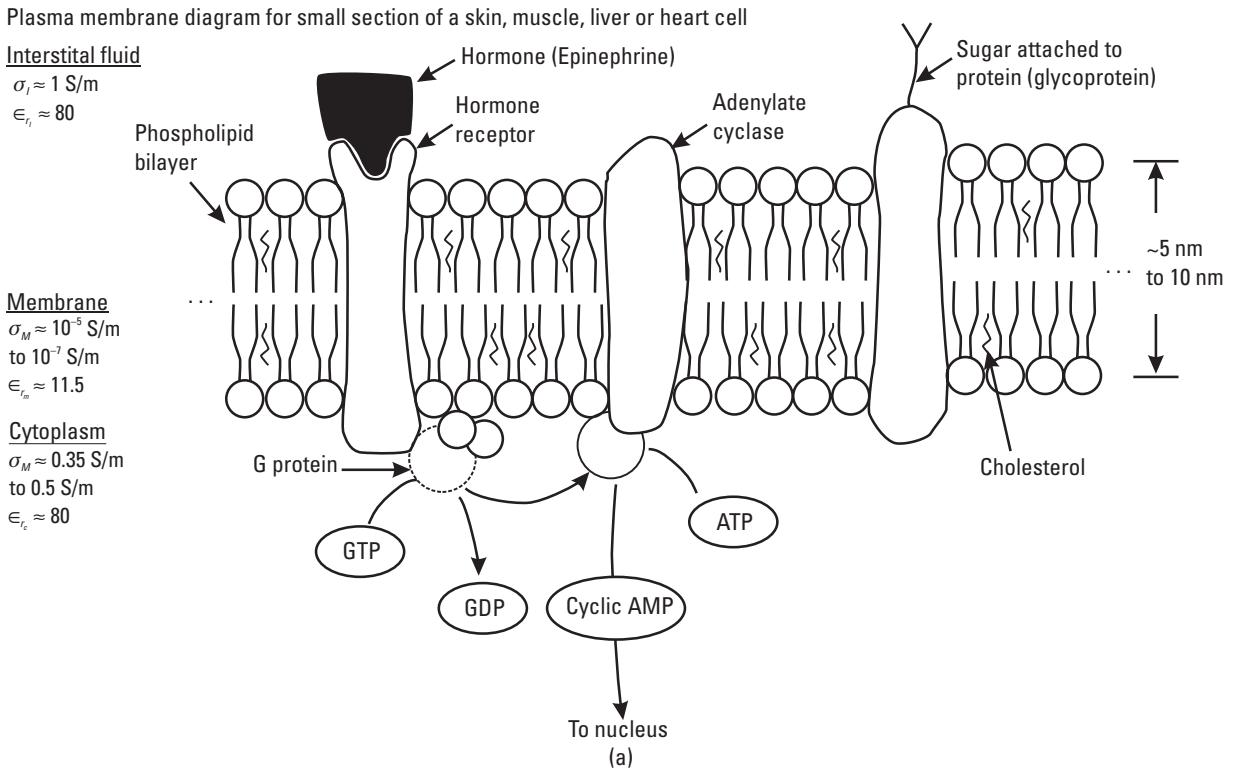


Figure 3.1 (a) Surface and near-surface region of a eukaryotic cell showing structures that contribute to the cell's electrical properties and electrical response along with part of a signal transduction pathway involving cyclic AMP. (b) Possible cell membrane receptor response to electrotherapeutic stimulation that could have an effect on cell metabolism, fatty acid production, heart rate, blood pressure, and so on.

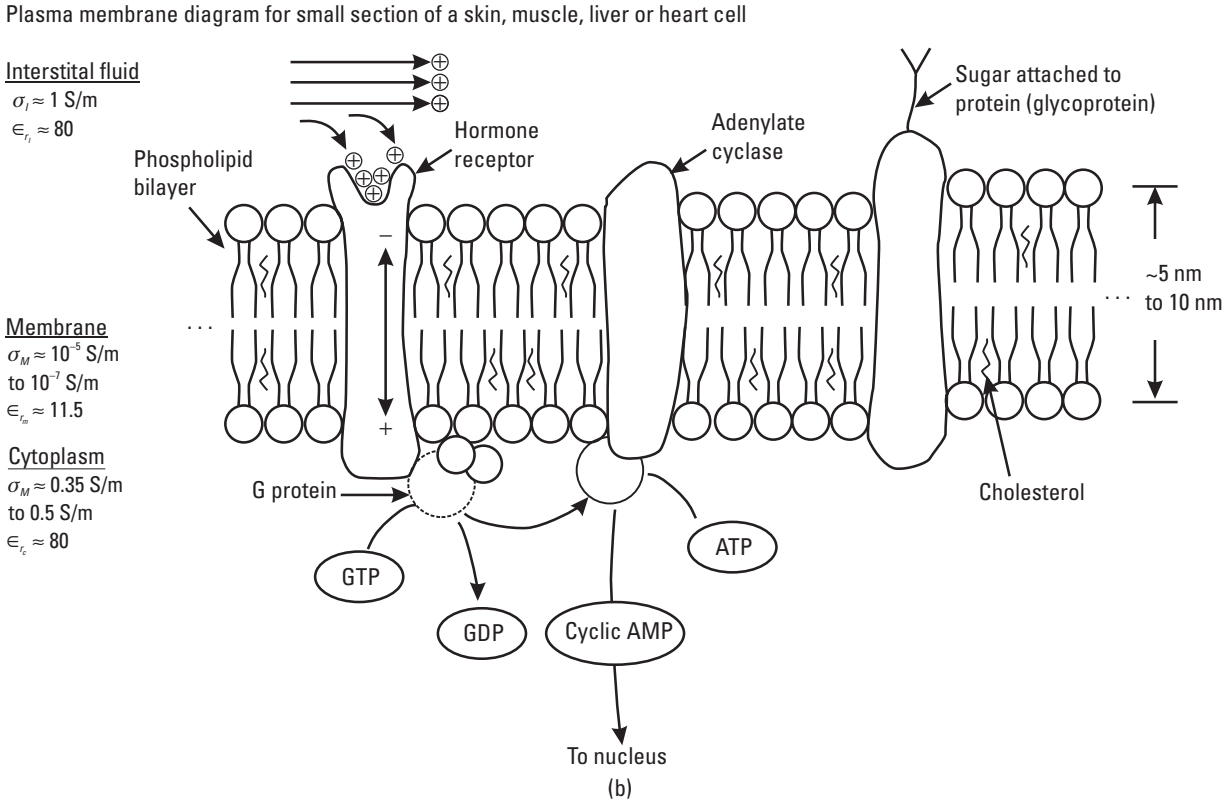


Figure 3.1 (continued.)

testing applications involving red blood cell cross-linking, IgG antibodies must be large enough to overcome the repulsive force between the red blood cells due to the effect of the zeta potential.

Naturally occurring electric field intensities in excess of 1 to 2 V/cm occur in wound healing, morphogenesis, and tumor growth processes. Electric field intensities at this level can promote directional migration for a variety of normal and malignant biological cells [9]. Electric fields applied to cell suspensions in vitro induce changes in cell shape that lead to directionally oriented cell growth [7]. For example, in suspension, human karatinocytes migrate toward the cathode region (galvanotaxis) with dc electric field intensities of 1 V/cm [10]. The mechanism appears to involve epidermal growth factor (EGF) receptors on the cell plasma membrane and physiological differences between a cell's leading edge compared to its trailing edge. In some cases, the asymmetrically activated signaling pathway appears to promote conformational changes and reorganization in the cell's cytoskeletal structure that are involved in cell motility [5, 10].

Electric fields of 1.5 to 4 V/cm can induce distinctive pre-angiogenesis responses in endothelial cells [11]. In addition, the distribution of certain cell membrane receptors can change with the application of externally applied electric fields. Cell receptors have been observed moving from the leading edge of the cell to the trailing edge, under the influence of externally applied electric field intensities of 1 to 5 V/cm [10].

The plasma membrane surface charge density associated with most cells is negative with values of approximately 0.02 C/m^2 to 0.2 C/m^2. Endogenous and exogenous electric fields (and any resulting current flow) can have significant effects on the symmetry of this surface charge, resulting in a change in membrane potential. This change in surface charge symmetry can influence the response of various voltage dependent ion channels [12, 13]. Electric fields can produce a redistribution of cell surface receptors and influence the flow of specific ions through plasma membrane ion channels [14, 15]. The molecular effects and ion transport variations associated with the application of endogenous and exogenous electric fields may be induced by physical, chemical, and electrical variations associated with charged cell surface receptors and ion channels. Any changes in the flow of ions through cellular ion channels can have significant effects on cellular metabolism, proliferation rate, cytoplasmic pH, mobility, cell cycle transitions, and apoptosis (programmed cell death). Levin cites a number of papers showing that ion channel function controls the proliferation rate for some cells that have a tendency to form malignant tumors, while membrane voltage variations appear to control the fate of the cell during differentiation [16].

Some research results have been reported concerning the effect of specific direct current intensity and current density levels on the proliferation of certain normal and malignant cells. Using relatively high electric field intensities (1

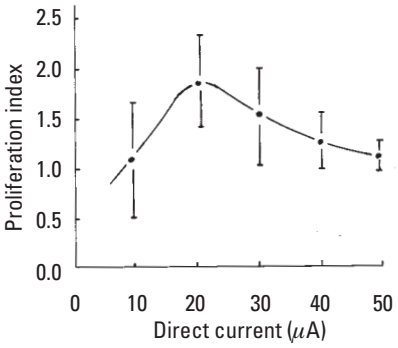
V/cm), very high direct current levels (approximately 2 mA), and exposure times of approximately 10 minutes or less, Viega et al. and Holandino et al. observed cell lysis, cell morphology variations, mitochondrial swelling, reductions in cell viability, and intense vacuolization in human leukemia K562 cells and mouse mastocytoma P815 cells [17, 18]. They propose that the effects of direct current on malignant cells are due, in part, to cathodic reactions generating superoxide radicals, and proliferation mediation due to the direct current inactivation of ribonucleotide reductase [18].

Chou and Yen et al. reported results on malignant mouse and rat fibrosarcoma cells and human KB cells over a range of current levels (400 μA to 2 mA) with exposure times of approximately 25 minutes to 4 hours. They reported a significant increase in malignant cell proliferation suppression and reduced malignant cell survival with the longer exposure times [19, 20]. They attribute the reductions in malignant cell survival and proliferation to the longer exposure times when the anode pH is lowest and the cathode pH is highest.

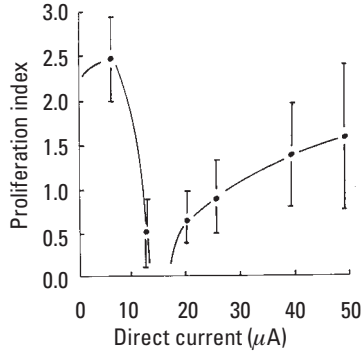
Lyte, Gannon, and O'Clock [21], O'Clock [22], and O'Clock and Leonard [23] reported a "window of suppression" for a number of different types of cancer cells (EL-4 lymphoma, IL-6 hybridoma, and retinoblastoma cells) at direct current levels that are much lower (less than 100 μA) and for much longer exposure times (10 to 20 hours). This very pronounced window of suppression does not occur for any normal cell lines tested. The window of suppression is the same for all of the cancer cells tested. The window occurs in a direct current range of 10 to 20 μA, and a range of current densities of approximately 900 to 1,800 $\mu A/cm^2$ [see Figure 3.2(a)].[1] They propose that the significant levels of malignant cell suppression, and the pronounced differences between the normal cell response and malignant cell response to direct current stimulation, could be influenced by (1) differences in plasma membrane receptors (oncogene derived proteins can be present on the cell membranes of the cancer cells) and differences in electrical response of those receptors, (2) differences or distortion in ion channel and Na^+/H^+ antiporter structure, and (3) media pH variations. The interaction between an electrical stimulus and a living cell can be quite complicated, involving changes in or interactions with cell proliferation [Figure 3.2(a)], cell physiology and morphology [Figure 3.2(b)], cell organelles, cell surface charge distribution, electrochemical effects (including internal and external pH), surrounding fluid medium, gene expression, and the wide range of activities moderated by cell plasma membrane receptors, ion channels, and ion pumps.

It is interesting to note that the suppression of cancer cell proliferation occurs close to the current densities associated with relatively high levels of cell metabolic activity for normal cells (~1 mA/cm^2).

1. The current density estimate could be high by a factor of 2 to 10.

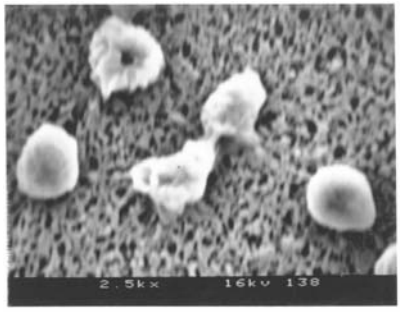


Proliferation index for normal retinal cells as a function of direct electrical current

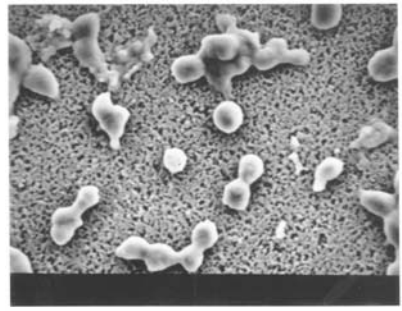


Proliferation index for malignant retinal (retinoblastoma) cells (approximately 750,000 cells/ml concentration) as a function of direct electrical current.

(a)



SEM micrograph (X 2.500) of EL-4 malignant lymphoma cells (initially at 10^6 cells/ml concentration) after being exposed to a current of approximately 9μA, necrobiosis zones start to appear. These are regions where noticeable changes in cell morphology occur, and portions of the malignant cell structures begin to disappear.



SEM micrograph (X 1000) of EL-4 malignant lymphoma cells (initially at 10^6 cells/ml concentration) after being exposed to a current of approximately 9μA and an electric field intensity of 0.5 V/cm for 24 hours. The EL-4 lymphoma cells are starting to lose the aggregation properties normally attributed to malignant cells.

(b)

Figure 3.2 (a) Proliferation characteristics for electrically stimulated normal cells and cancer cells showing a pronounced window of suppression for the cancer cells (retinoblastoma) and a very different proliferation characteristic for healthy retinal cells. (b) Apparent necrobiosis along with changes in aggregation properties for electrically stimulated malignant cells. (Courtesy of the IABC Foundation, Palm City, Florida. Also see [23].)

From an electrical standpoint, and under specific conditions, biological cells can be analyzed and treated as isolated dielectric spheres, closed shells

surrounded by conductive media (i.e., colloids), isolated conductive elements, or interconnected conductive entities. For analysis and modeling purposes, the inner region of the cell (cytoplasm) is often treated as a region full of a saline-like liquid containing organelles, nucleus, and a cytoskeleton structure. The cytoplasmic conductivity is often specified as approximately 0.3 to 1.0 S/m with a cell plasma membrane conductivity in the range of 10^{-7} to 10^{-5} S/m and an interstitial fluid conductivity of 1.0 S/m [24].

As previously indicated, the surface charge density of a typical cell is often considered to be in the range of 0.02 to 0.2 C/m^2 (usually, negative). Long chain glycoprotein structures (such as N-acetylneuroaminic acid), extending beyond the cell's plasma membrane, contribute to the negative surface charge density. It is estimated that there are approximately 100,000 to 600,000 of these glycoproteins on the surface of each red blood cell. They contribute to the red blood cells relatively high surface charge density (approximately 0.1 C/m^2). Also contributing to the negative surface charge density of a typical cell membrane are the glycolipids, phosphoglycerides, and phospholipids.

Considering the cell as an electrically conductive and responsive unit, made up of a variety of molecules that are involved in ion and electron transport; it should be no surprise that electric fields have the ability to influence cell motion (galvanotaxis), cell shape, cell polarity, and cell growth orientation (galvanotropism).

Electric fields can move or stimulate cell membrane receptors. Electric fields can also have an effect on membrane ion channel characteristics.

Combining these facts with results that reveal the effect of low-level electric currents on the production of certain phosphorylated nucleotides (in this case, adenosine triphosphate), it is clear that exogenous electric currents, voltages, and electric fields provided by electrotherapeutic devices can have significant influences on cell structure, movement, metabolism, replication, differentiation, and proliferation.

Ion flow is a dominant electrical current mechanism associated with endogenous electric fields and exogenous electric fields. And as ions form, accumulate, move, and bond with other substances in the cellular environment, these ionic processes can influence many local electrical transport-transfer mechanisms in cell membranes, cell receptors, ion channels, nucleus, and cell organelles.

Now, what if the cytoplasm of the cell is a gel? Under this condition, the gel would be able to inhibit sodium ion penetration into the cytoplasm (because sodium ions have large hydration shells) and possibly minimize the ion pumping workload. The phase transitions that promote volume changes in a cytoplasmic gel could contribute significantly to a variety of cell characteristics and processes including motility and secretion [25]. The electrical properties of a cell with a cytoplasmic gel could be highly variable. Electrical parameter studies for a

variety of gels indicate that a variation of just a few percent in gel liquidity can produce significant changes in electrical conductivity and dielectric constant. Considering the cytoplasm as a liquid electrolyte, the electrical conductivity is often specified within the range of 0.3 to 1.0 S/m. As the cytoplasm becomes more of a gel, the cytoplasm's conductivity would tend to decrease to levels significantly lower than 0.3 S/m. Variations in cell cytoplasm conductivity and dielectric constant can have significant effects on the impedance and frequency response of associated tissues.

3.2 Electrical Properties of Tissues

Considering the conventional cell model, the structure of biological tissues includes a variety of cells, with many of them interconnected by gap junctions (allowing the cells to electrically and chemically communicate with each other) or buffered by fluid. Based on this, one would expect biological tissues to be electrically conductive. Let us assume that tissue can be represented by a series/parallel cascade of cells that are approximately 20 μm in diameter and spaced approximately 1 to 2 μm apart. For ionic current at low frequencies, we will assume that most of the ionic transport occurs only within the interstitial fluid spaces between cells (we will modify this assumption later on in Chapter 7). Information given in Section 3.1 indicates that interstitial fluid conductivity is approximately 1 S/m, or 0.01 S/cm. Tissue resistance, R, can be expressed as $R = l/\sigma A$ (where l is length, A represents cross-sectional area, and σ represents electrical conductivity). Using this relationship, we can estimate the resistance of a 75-cm-long, 3-cm-wide, and 0.5-cm-thick section of tissue. These tissue dimensions are relevant for tissue sections associated with many electrotherapeutic treatment protocols. Calculations for this tissue section reveal a low frequency (essentially dc) tissue resistance value in the range of approximately 5 to 15 kΩ, based on a 0.01-S/cm interstitial fluid conductivity, 1- to 2-μm interstitial space dimensions between cells, and a variety of meandering conductive pathways around the cells. Electrode-tissue interface polarization effects can produce apparent or measured resistance values that are significantly larger than the calculated value of R.

Knowing the current and applied voltage values associated with various electrotherapeutic devices, and using Ohm's law to calculate tissue resistance, apparent or measured patient tissue resistance values at very low frequencies and relatively low microcurrent levels are usually in the range of 2.5 to 100 KΩ, with most of the values in the range of 7 to 40 KΩ. The impedance values will depend upon the moisture content of the tissue, voltage drop at the probe tissue interface (polarization effects, which can be substantial), quality of the probe or electrode contact and frequency. Therefore, based on actual

measurements, we may conclude that we have a reasonably good model for tissue resistance, where values calculated are fairly close to resistance values measured. However, that conclusion would be wrong. In some situations, involving bioelectric phenomena, a simple model will often provide numbers that are reasonably close to measured data. But many times, when conditions change, it becomes evident that the model is really not appropriate, or it is massively oversimplified.

Just stringing a bunch of cells together and mathematically treating them as a long chain of series/parallel resistances does not provide an accurate model for tissue impedance. There is much more to consider. Also, it is important to recognize the type of current that is involved in these biological processes. Are we considering the current to consist of ion flow, electron flow, or a mix of the two? For this example, the primary contribution to electrical current involves the flow of ions.

A model based on bioelectrical impedance analysis (BIA) has been developed by A. L. Thomasset for various types of biological tissue [26, 27]. On a microscopic scale, Thomasset models the tissue as a group of closely spaced cells separated by interstitial fluid (shown in Figure 3.3). Electrical conduction is dominated by a drift current [or direct current involving the flow of ions, $J = I/A = \sigma \mathrm{E} = pq\mu \mathrm{E} = pqv_D$, from (2.6)]. At frequencies between 1 and 10 kHz, most of the ion current does not "penetrate" the cells. For the most part, the current flow involves meandering conductive pathways, in the interstitial fluid, around the cells (as was assumed in the previous example).

At the lower frequency range, the cells are treated almost as if they are isolated dielectric spheres. The resistance of the interstitial fluid is designated as R_S, and the collective effect of each interstitial fluid pathway can be expressed as a simple resistance. At frequencies above 10 kHz, ionic displacement current (often referred to as Maxwell's pseudo-current) becomes significant. The displacement current density, J_{DISP}, associated with the plasma membrane capacitance, C_M, is determined by time rate of change of electric flux density, D_M, or electric field intensity, E_M, associated with the plasma membrane, area, A_M, and membrane thickness, d_M:

$$J_{DISP} = \partial D_M / \partial t = \partial \left(\varepsilon_R \varepsilon_O \mathrm{E}_M \right) / \partial t = \left(\varepsilon_R \varepsilon_O \right) \partial \mathrm{E}_M / \partial t \quad \text{(if } \varepsilon_r \text{ and } \varepsilon_O \text{ are time-invariant)} \tag{3.1}$$

where $J_{DISP} = J_{DO} e^{j\omega t} = (I_{DO}/A_M) e^{j\omega t}$, $\mathrm{E}_M = \mathrm{E}_{OM} e^{j\omega t}$, $\mathrm{E}_{OM} = V_{OM}/d_M$, and membrane capacitance $C_M = (\varepsilon_R \varepsilon_O) A_M / d_M$. The following equations can be derived from the relationships between the displacement current and electric field intensity associated with the cell's plasma membrane:

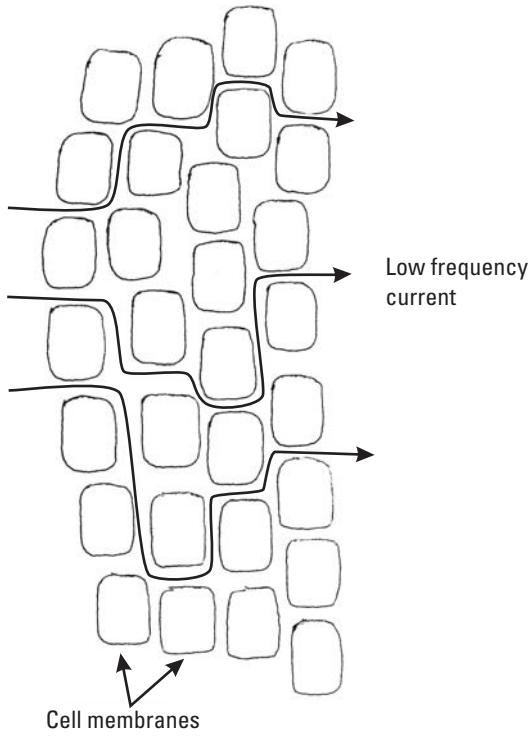


Figure 3.3 (a) Cells and interstitial spaces in tissue, meandering electrical current pathways for low-frequency currents, and electronic filter circuit analog. (b) Pathway for higher frequency electrical current through cells (displacement current). (c) Tissue impedance characteristics as a function of frequency.

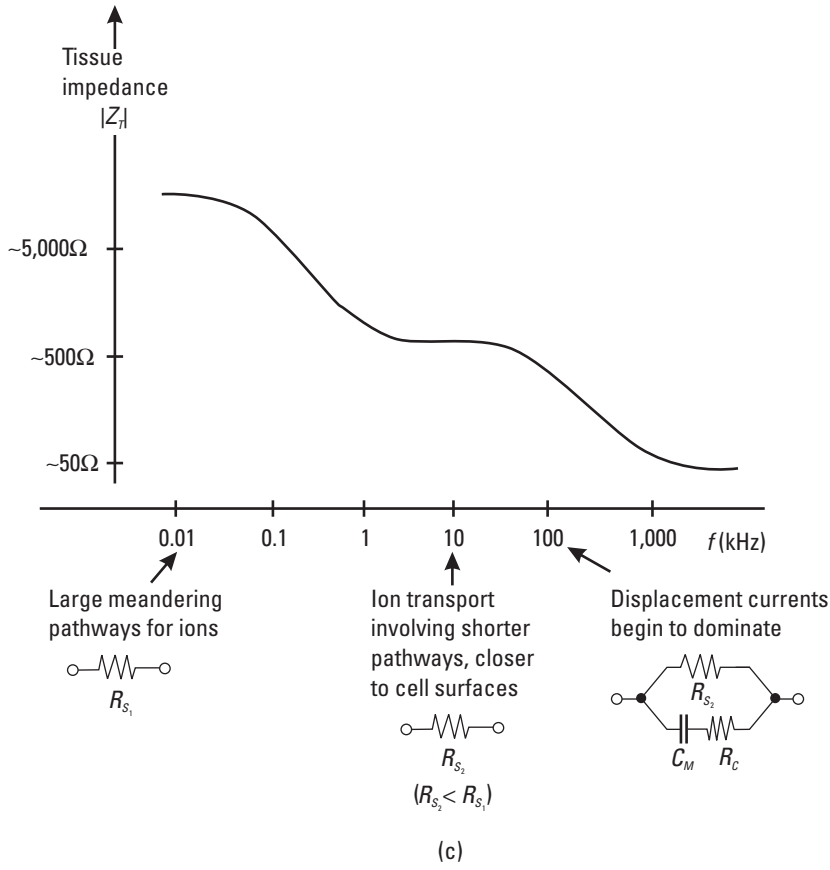


Figure 3.3 (continued.)

$$J_{DISP} = J_{DO}e^{j\omega t} = \left(I_{DO}/A_M\right)e^{j\omega t} = \left(\varepsilon_R\varepsilon_O\right)\partial \mathrm{E}_M/\partial t$$
$$= \left(\varepsilon_R\varepsilon_O\right)\left(j\omega\right)\mathrm{E}_{OM}e^{j\omega t} =$$
$$\left(C_M d_M/A_M\right)\left(j\omega\right)\left(V_{OM}/d_M\right)e^{j\omega t}$$

Therefore, with respect to the reactive part of the membrane impedance, Z_{MR},

$$Z_{MR} = V_{OM}/I_{DO} = 1/j\omega C_M = 1/2\pi f\left(C_M\right) \tag{3.2}$$

In the case of the lower frequency drift current, the product of the capacitance of the cell's plasma membrane and the frequency yields an impedance term that is too high to support ionic displacement currents. Therefore, at the lower frequencies, a significant portion of the drift current cannot penetrate the

cell membrane. At very low frequencies, the slow moving ions are easily "scattered" and they follow a relatively high resistance, R_{S1}, very pronounced meandering interstitial fluid pathway around the cells, as shown in Figure 3.3(a). Then, as the frequency increases, the ions tend to follow a pathway closer to the surface of the each cell. The distance traveled is less than it is for the much lower frequencies because this particular pathway does not involve the very pronounced level of meandering. The shorter distance traveled decreases the total resistance of the interstitial fluid pathway, R_{S2}, for these somewhat higher frequencies. As the frequency increases further, the product of the cell plasma membrane capacitance, C_M, and frequency, $2\pi f$, produce an even lower membrane impedance, Z_{MR}, and the resulting displacement current appears to "penetrate" the cellular volume, as shown in Figure 3.3(b). As the frequency increases, the reactive component of the membrane impedance (Z_{MR}) approaches zero and the total conductive pathway impedance decreases to a value that is equal to the parallel combination of the interstitial fluid resistance, R_{S2}, and the resistance of the cytoplasm, R_C, as shown in Figure 3.3(c).

The resistance or impedance values shown are reasonably close to the crude estimates previously calculated for meandering ion transport through the cellular interstitial spaces at very low frequencies. In general, tissue impedance is quite high at low frequencies. Then, as frequency increases, the tissue impedance decreases under the influence of the tissue's equivalent R-C filter circuit, shown in Figure 3.3(c) of Thomasset's model.

For moistened tissues, the impedance can decrease more than two orders of magnitude from the lower frequency range to the higher frequency range. As previously mentioned, if the cytoplasmic fluid varies between the liquid and gel state; and undergoes phase transitions as a result of electrical, thermal, chemical, or mechanical stimuli, small variations in a variety of stimuli and/or parameters could produce significant variations in the volume, dielectric constant, conductivity, and resulting impedance associated with the cytoplasm. Under these conditions, the tissue impedance characteristic of Figure 3.3(c) would exhibit significant variations as the cytoplasm undergoes a transition from liquid to gel, and then exhibits the effects of gel-gel phase transitions.

Thomasset's impedance data for biological tissue strongly correlates with total volume of body water and total volume of extracellular fluids. Water equilibrium varies when the body is at rest, active, aging, or in a diseased state. Low-frequency data often shows impedance levels for cancerous tissue that are 2 to 3 times higher than the impedance of adjacent healthy tissue. On the other hand, for relatively long time periods, 5-kHz impedance plots indicate that the impedance of cancerous tissue decreases significantly compared with the impedance of normal tissue. Time-varying impedance values can produce highly conflicting results between different research efforts. This change in impedance over time could be attributed to a combination of reduced oxygen storage capacity,

degraded cell membrane structure, impaired cell membrane function, and water migration in the cancer tissue.

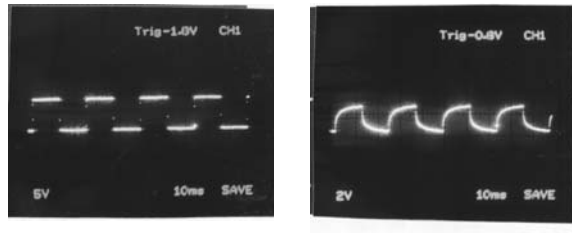
Bioelectric impedance analysis can yield useful diagnostic information on the condition and state of the body under diverse physiological or clinical circumstances [27]. A number of techniques have been proposed, using measurements of impedance and dielectric constant, to develop imaging techniques that detect abnormal tissues, or cancerous tissues, as an alternative to conventional mammography [28].

3.3 Impedance Considerations in Device and Protocol Design

Impedance variations associated with a variety of elements in the conductive pathway of the electrotherapeutic device can affect the therapeutic efficacy of the device and produce serious reliability problems. As diseased tissue is being treated with an electrotherapeutic device, polarization effects, the combination of healing processes associated with infection, the movement of water, and variations in electrode contact quality can produce significant apparent impedance variations over a 10- to 20-minute treatment duration. An apparent patient load impedance decrease from approximately 80 to 35 kΩ can occur over a relatively short period of time with microcurrent therapy. Apparent impedance variations often become more extreme due to patient age, the effects of prescription medications, patient treatment position (sitting up, lying down), contact quality (electrode pressure, drying of contact gel or liquid, electrode corrosion, contact point location, and so on), and patient dehydration (common in elderly). The electrotherapeutic device must be capable of delivering a relatively constant current that does not vary significantly with impedance variations.

Figure 2.5 showed that applied currents can alter tissue structure, which can have a significant influence on tissue impedance. In addition, Thomasset discusses how oxygen and carbon monoxide exposure can change normal and diseased tissue impedance levels [26, 27]. For most electrotherapy applications, as previously indicated, tissue impedance can undergo significant variations over time. This time-varying characteristic will have an impact on device and treatment protocol design.

Many electrotherapy applications involve voltages and currents with frequencies less than 20 Hz. Due to the frequency response characteristics of tissue, beyond 40 Hz, the dominant odd harmonics will be attenuated. Rectangular output voltage waveforms will become severely distorted. Figure 3.4 provides an indication of the kind of square wave distortion that can occur, even at very low frequencies of 100 Hz or less, when applied to biological tissue.



(a) (b)

Figure 3.4 (a) Electrotherapeutic device output voltage waveform (40 Hz) with resistive loading. (b) Output voltage waveform (40 Hz) for the same electrotherapeutic device with a section of tissue as a load. The distortion is due to the influence of the tissue's frequency response characteristics.

3.4 Electrical Properties of Organs

Some of the electrical properties of an organ, such as the heart, depend upon the structure and interconnections associated with specific cells. With ion concentration differences between the cellular cytoplasm and external interstitial fluid, an electrical potential difference is established between the inside and outside of the cell membrane. For example, a proper stimulus can induce a change in the membrane potential to generate a brief and regenerative "all-or-nothing" action potential that propagates from cell to cell along a heart muscle fiber. Intercalated disks between cells help to synchronize heart muscle contractions. Gap junctions formed between the various branched networks of cells provide a low resistance path for current to flow, allowing the effects of the propagating action potential to spread uniformly from cell to cell and fiber to fiber [29]. The process of depolarization that produces the action potential in one group of heart cells quickly propagates, producing depolarization of neighboring interconnected heart muscle cells, allowing all of the cells to contract together as a coordinated unit.

With proper stimulation, nerve fiber also generates an action potential that involves a different looking waveform compared with the action potentials of heart muscle fibers. A nerve fiber action potential (starting with a depolarization) results from voltage-dependent changes in membrane permeability for specific ions (ionic hypothesis). Using a network of neurons (where each neuron consists of a soma region, dendrites, and/or nerve axon), the nerve fiber action potential can travel relatively long distances. In this case, the electrical properties of the heart and nervous system are essentially due to their unique and interconnected cellular structures. But the action potentials of the cardiovascular and nervous system represent only a small sample of the electrical and electrochemical processes involved with healing and regulation in biological systems.

When organs are interconnected, some of the electrical properties that influence their responses may be dominated by the fluids that are being processed or transported within the organ system. Using his theory of biologically closed electric circuits (BCEC), Björn E. W. Nordenström shows similarities between ion current flow occurring in an acid-base battery and a BCEC ion current flowing in a system of interconnected organs. In one case, the BCEC ion current flow occurs between certain regions located in the stomach and upper intestine (acidic—pH as low as 2) and the gall bladder (basic—pH of bile is between 7.6 and 8.6) [30].

Within the BCEC paradigm, Nordenström also utilizes a vascular interstitial closed electric circuit (VICC) model, involving a urinary-vascular closed circuit (as shown in Figure 3.5), to describe the results obtained with the effects of direct electric current on renal output [31]. With the renal ureters operatively ligated, Nordenström applied a dc voltage (up to 9V) between the ureters that are connected to each kidney. A direct electric current is injected through the

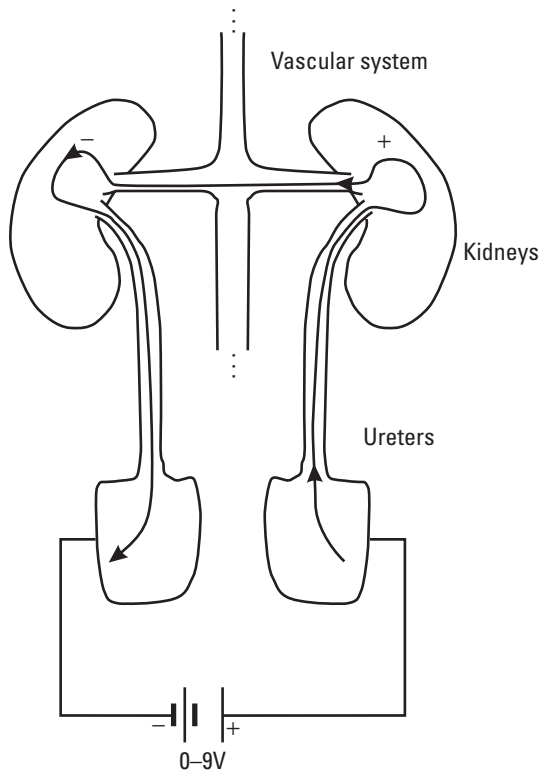


Figure 3.5 Experimental arrangement for evaluation of BCEC mechanisms in the renal system. Fluid excretion is enhanced by electro-osmotic flow of water toward the cathodic (negative electrode) kidney region.

kidneys and associated vessels. Nordenström then describes an electro-osmotic flow of water toward the cathodic kidney region. Fluid excretion was enhanced through the kidney associated with the negative electrode (cathodic). Fractional sodium excretion by the cathodic kidney was increased 80%.

Robert O. Becker proposes a closed loop negative feedback dc (or low frequency) analog communication-control system involving the brain and the perineural cells (glial cells and Schwann cells) [32, 33]. He maintains that this system involves essentially analog signals (slowly varying) and analog controls. The perineural cells are associated with every part of the nervous system and appear to be semiconducting. Becker indicates that these cells are appropriately structured and distributed to integrate bodily processes. They enable the body to sense the type and extent of an injury, and they transmit the injury current to the central nervous system. Part of the dc signal is sent to the brain as a pain signal. The remainder of the signal is routed to a more primitive region of the brain where a similar dc output signal is sent to the injury site to initiate or assist in the healing process. In this system, when an injury occurs, dc electrical signals carry information that injury has occurred along perineural cell pathways or acupuncture meridians to the brain. If the currents are dc (essentially, non-time varying), the biological dc electrical system and circuit that Becker proposes must be closed. Becker's dc communication-control system appears to be another example of a proposed BCEC (or system) involving major organs in closed loop structures.

At the cellular and tissue level, electrical parameters are strongly dependent upon bonding, differences in ion concentrations over small regions, and microscopic cell-tissue structure. Using simple closed electric circuit or closed system models, it is easy to show that some of the electrical properties associated with organ systems strongly depend upon (1) macroscopic structure, (2) nerve and vascular coupling, (3) the type of fluid constituents associated with each organ, and (4) pH differences between the various fluid constituents in each organ.

Instead of focusing on any differences of opinion, the field of electrotherapy would be better served if the complementary aspects of Dr. Becker's and Dr. Nordenström's views were emphasized. By themselves, the two men are incredibly brilliant, innovative, and creative medical doctors and researchers. However, by combining or integrating their work, they become much more than the sum of their individual accomplishments. In his book *Cross Currents* [33], Dr. Becker's negative comments about Dr. Nordenström's BCEC theories and therapeutic technique in the treatment of cancer appear to be premature. The negative comments may have done some damage to the credibility of both men. Dr. Becker could have profited by waiting a little longer, being a little more moderate with his impressions, comments, and criticisms. Dr. Nordenström's technique, utilized in the treatment of cancer, has been very successful and has been applied to more than 16,000 cancer patients in a

number of countries including China, Sweden, Germany, and Australia. Dr. Nordenström's technique has also been introduced in Korea and Latin America. There is no doubt about the efficacy and relative safety of Nordenström's electrotherapeutic technique in the treatment of cancer.

Dr. Becker and Dr. Nordenström exhibited very different personalities. But their work shows that they were both well versed in the scientific method. They also had a lot in common in the response they received from colleagues in the medical profession. The more successful they were, the more jealousy, theft of their research ideas, and management stonewalling they encountered.

Dr. Becker continued to prove that the standard medical dogma was significantly flawed because of its failure to address the relevance of bioelectricity and the impact of bioelectric phenomena on regeneration, cell dedifferentiation, and certain aspects of fracture healing. As time went on, he began to see some of his research ideas copied by people who visited his lab. Then, as interest in his work and results increased, Dr. Becker began to encounter problems with lack of support within the Veteran's Administration. Dr. Becker also lost management support when he refused to respond to pressure by certain department heads to engage in a practice that is nothing more than scientific fraud. Some of these administrators demanded that their names be included as co-authors of Dr. Becker's research papers, in spite of the fact that they made no scientific contribution to the effort.

As Dr. Becker became more successful in achieving results strongly indicating that certain elements of accepted medical dogma were incomplete and/or incorrect, he was invited to present his results at medical conferences and seminars. At the same time, attempts were made by management to reduce Dr. Becker's position and close his lab. Internal reviews of his work became more critical and conflicting. In addition, as Dr. Becker and his colleagues revealed more and more information concerning the hazards of electromagnetic radiation and power line dangers, the pressure increased from the Department of Defense to back off. Dr. Becker was threatened with audits, trumped-up charges of financial misdeeds, and a ruined career if he continued revealing facts concerning the biological impacts of nonionizing radiation. Eventually, the influence of political pressure dominated. The support for Dr. Becker's successful research effort was terminated and his laboratory facilities were shut down [32].

Dr. Nordenström encountered similar resistance from his medical colleagues. Initially, he was allowed to administer his electrotherapeutic technique to cancer patients at Karolinska (Stockholm), who were considered terminally ill, and only had weeks or a few months to live [34]. One of his patients was a nurse who worked at Karolinska. Many of his colleagues assumed that, based on accepted medical dogma, Dr. Nordenström would show a gallant effort, but eventually fail miserably. But the unthinkable happened. A surprising number of the terminally ill patients, who had only weeks or a few months to live, went

into remission after three or four of Dr. Nordenström's electrotherapeutic treatments. Dr. Nordenström's success was becoming an embarrassment to many of his colleagues. After several treatments by Nordenström, some of the terminally ill patients went back to work (including the nurse).

Dr. Nordenström was showing better results with electrotherapy, administered to terminally ill cancer patients, than some of his colleagues were able to achieve with early stage cancer patients receiving conventional chemotherapy, radiation therapy and surgery. With all of this success, one would assume that more cancer patients would be given the opportunity to receive Dr. Nordenström's electrotherapeutic treatment. But just the opposite happened. As time went on, Dr. Nordenström received less encouragement and support for his work at Karolinska. Finally, in order to have electrotherapy administered to cancer patients on a large scale, Dr. Nordenström had to introduce his technique to medical doctors in China.

One can almost envision the spirit of William Harvey shaking his head and saying, "Nothing has changed for men and women of vision in the world of medicine. If you dare to conflict with medical dogma, please protect your research records, and protect yourselves. Carry a dagger!"

3.5 Nordenström's Theories: BCEC and NEAT-EChT

During the 1950s, Dr. Björn Nordenström became interested in the streaks, spikes, and coronas that he saw in X-ray images of lung tumors (as shown in Figure 3.6). When Dr. Nordenström discussed these images with other physicians, many of his colleagues saw nothing. Others attributed the phenomena to

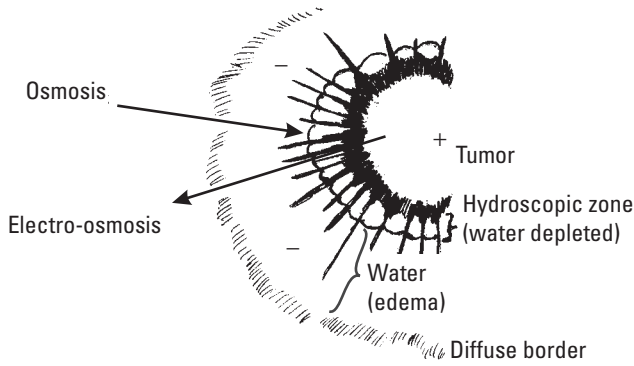


Figure 3.6 Drawing of a lung tumor necrosis with streaks, spikes, and corona structures in X-ray images as described by Nordenström.

artifacts in the image. In 1965, Dr. Nordenström began a scientific investigation into the subtle phenomena that he observed in X-ray images [35, 36].

After years of very careful experimentation and analysis, Dr. Nordenström came to the conclusion that various electrical phenomena were associated with the streaks, spikes, and coronas that were often present in X-ray radiographs. From his observations, analysis, and measurements, Dr. Nordenström developed a theory involving continuous energy circulation in living systems. In his theory, Dr. Nordenström describes field and energy circulation accompanied by the cotransport of charged species (ions and electrons) forming continuously circulating electric currents in the human body. These currents are produced and maintained within various BCEC pathways. Nordenström's BCEC model for a malignancy is shown in Figure 3.7. The BCEC currents are moderated by the condition of the living system, ion production, and ion transport, and they participate in maintaining equilibrium and healing [36, 37]. Macroscopic BCEC pathways are discussed in Section 3.4. In this section, a BCEC pathway that is more localized and more related to the phenomena that Dr. Nordenström observed in his X-ray radiographs is described.

Dr. Nordenström realized that by augmenting the healing process normally associated with the naturally occurring BCEC pathways in the human body, electrotherapeutic techniques could be developed (or improved) to treat a variety of disorders including cancer, nervous system disorders, and cardiovascular disease. Utilizing his electrophoretic model, Dr. Nordenström developed an electrochemical therapy (EChT) technique that has been proven to be very effective in the treatment of cancer. In fact, EChT has been successfully utilized in situations where radiation therapy and chemotherapy have proven to be ineffective in treating the cancer condition and/or when surgery has been ruled out as an option.

The term electrolytic ablation therapy or electrolytic ablation of tumors (EAT in either case) would appear to be a more appropriate term for Nordenström's technique. However, it often appears that this term is being either captured or misused by some practitioners in order to take credit for the development of this technique, or to push Dr. Nordenström's contributions to the background. Therefore, in reference to EChT and EAT, from here on, this book will refer to the technique as Nordenström's Electrolytic Ablation Therapy (NEAT) and the two acronyms will be combined as NEAT-EChT. This designation is not too clumsy, and it gives appropriate credit to the man who evolved and improved an electrotherapeutic method that has been under investigation for the past 140 years.

Unlike certain chemotherapy or radiation therapy protocols, NEAT-EChT does not depend upon the cell cycle for therapeutic efficacy. NEAT-EChT promotes autolysis and tumor necrosis by reducing the tumor pH (increasing acidity) and elevating the pressure in the cancerous tissue by anodic

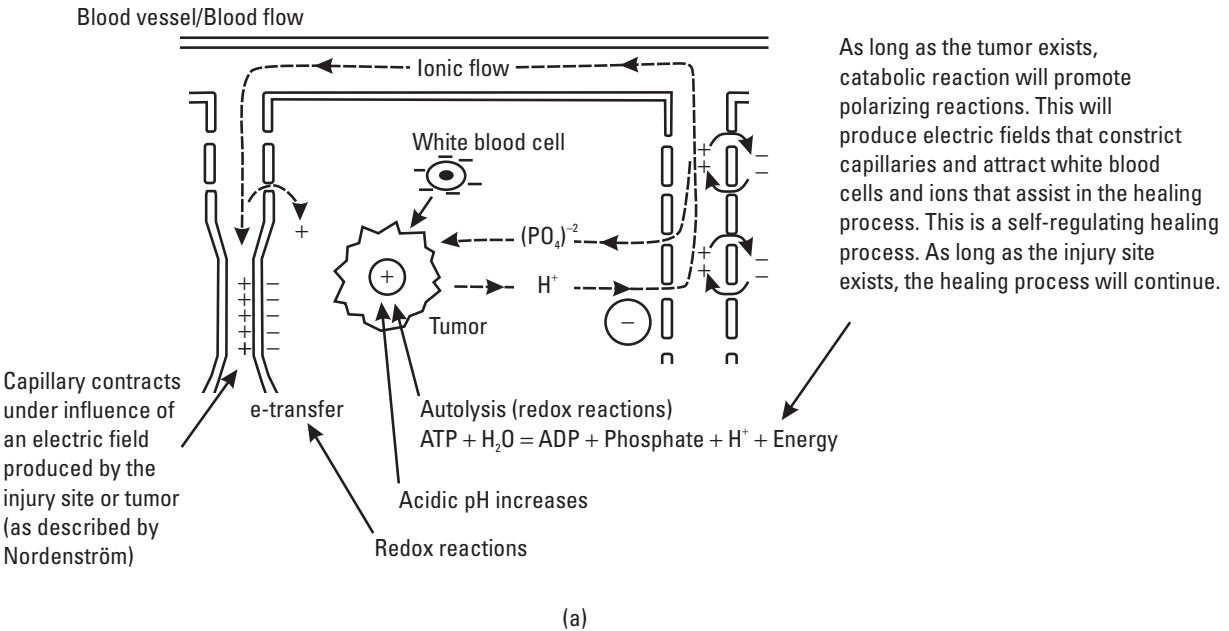


Figure 3.7 (a) A BCEC for the electropositive state of a tumor. In addition, water (not shown) is flowing into the tumor by osmosis and out of the tumor by electro-osmosis. (b) The electronegative state of a tumor. In this state, the transport of the fast moving, relatively light hydrogen molecules leaves the center region of the tumor temporarily negative because the slower moving and heavier negative ions remain. (c) Variation of tumor site potential alternating between electropositive and electronegative due to differences and variations in ion transport and ion production over time.

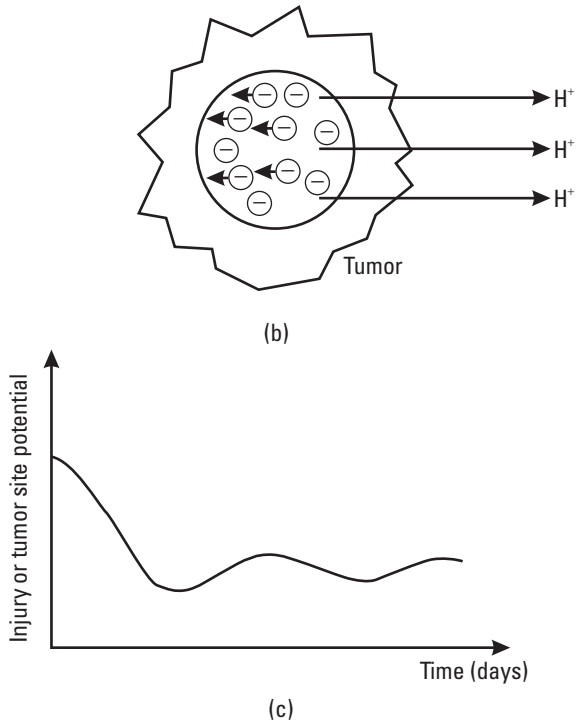


Figure 3.7 (continued.)

and cathodic gas formation (which destroys tumor structure). At the cellular level, NEAT-EChT appears to have an effect on cell membrane receptors, ion channels, and antiports that assist in regulating metabolic processes, cell proliferation, differentiation, aggregation, transcription, cell pH, cell membrane potential, cell necrosis, and apoptosis.

By inserting a positive electrode at the center of a tumor, and a set of negative electrodes in the normal tissue surrounding the tumor, the exogenous applied voltage of the NEAT-EChT technique (shown in Figure 1.2) assists and enhances the naturally occurring endogenous voltages associated with the processes taking place in the tumor. With respect to the positive electrode at the center of the tumor, water is drawn away from the tumor's central area by the process of electro-osmosis, and cancer-fighting white blood cells are attracted to the tumor site. NEAT-EChT complements and supports the healing processes that occur naturally with malignancies.

Some medical researchers have stated that Nordenström's technique is not significantly different from earlier electrotherapeutic techniques utilized in the treatment of cancer. Others disagree with that statement, for good reasons. Nordenström provided a level of analysis and a closed loop system model

description that is very useful. He was the first to combine all of the scattered theories and experimental work that had been done previously, and relate them all to regulation and healing in the human body [34]. Nordenström's BCEC theory provides a system model that agrees quite well with fluctuations in electrical parameters observed during the healing process associated with a malignancy. His model also provides an excellent platform to explain the fast response times and high degree of "directed flow" for ions, metabolites, and white blood cells associated with immune system response. In fact, using a few relationships from electric field theory and fluid mechanics, Nordenström's electrically driven BCEC model provides an excellent foundation to overcome the limitations that certain diffusion models have in predicting fast immune response times.

The efficient and timely transport of specific ions, charged molecules, and white blood cells is very important in healing and regulatory processes. As living systems evolved from diffusion-based single-cell life forms to larger multicellular living systems, circulatory systems had to be incorporated into the larger multicellular systems enabling nutrients and immune system components to reach a larger number of remote locations. Some diffusion-limited processes for individual isolated molecules, nutrients, and immune system components are much too slow and imprecise for applications at distances approaching 1 cm. With respect to the simple (unfacilitated) translational Brownian diffusion model, the diffusion speed for an atom or molecule suspended in a liquid can be estimated from the following equation:

$$\tau_D = L^2/2D \tag{3.3}$$

where L is the diffusion distance, D is the diffusion coefficient, and τ_D is the diffusion time required to travel the diffusion distance. A 0.4-nm isolated glucose molecule, with a diffusion coefficient of 7.1×10^{-6} cm^2/sec (in water), requires more than 10 minutes to travel just 0.1 cm by diffusion. An 8-μm white blood cell would require much more time to travel the same small distance by simple diffusion. Therefore, self-regulating fast fluid-flow circulatory systems (cardiovascular and lymphatic) are required to allow substances to travel long distances over relatively short periods of time. The fluid transport capabilities of the cardiovascular system provide velocities of approximately 400 cm/sec (aorta) to velocities less than 10 cm/sec (capillaries). The velocities provided by the cardiovascular system are approximately 1,000 to 50,000 times faster than the velocities that could be provided by a system where transport is limited to diffusion processes.

However, in order to sustain life, self-regulating fast fluid-flow circulatory systems have limited capabilities. The cardiovascular and lymphatic system can deliver nutrients and immunologically important cells and substances to specific regions. However, the precise location where the nutrient is needed or where the

injury is located can involve additional distances of 0.05 to 0.1 cm from the vascular or lymphatic component. As previously shown, diffusion is much too slow to deliver these substances to the exact location where they are needed. Immune system reaction times, certain components of endocrine system response, and the various adaptation mechanisms associated with living systems are much faster and more precise than some of the standard physiological system models involving circulation and chemotaxis would predict. Another level of transport/circulatory systems need to be considered to explain the accuracy and precision associated with the movement of nutrients, white blood cells, and metabolites to specific locations involving wound healing processes, fracture repair, and tumor regression/remission [38].

The effective and timely transport of ions and molecules is critically important in the process of healing and regulation. Mathematical models relating electronic and ionic diffusion and drift current density indicate that relatively small voltages, in excess of 10 mV, can overcome random drift tendencies for ions and small molecules and influence the direction of migration or transport in a liquid. For instance, considering an ionic flux (current density, J) in a cytoplasmic or interstitial fluid,

$$J = -qD\nabla\rho + q\rho\mu\mathrm{E} \tag{3.4}$$

Since $\mathrm{E} = \nabla V$,

$$J = -qD\nabla\rho + q\rho\mu\nabla V \tag{3.5}$$

where q represents charge, ρ represents the concentration of charged ions, D is the diffusion constant, V is electric potential associated with the injury site, μ represents ion mobility in cytoplasmic or interstitial fluid, and E is the electric field produced by the injury site [38]. Considering Coulomb's law for charge and Gauss' law for electric fields, the electric field and electric potential are both a function of the charge density of the injury site, the dielectric constant of the fluid medium, and distance. The value of electric field intensity (E) that counteracts the effects of diffusion can be calculated by setting the current density (J) to zero in (3.5). Rearranging terms, we find

$$\partial\rho/\rho = \mu\mathrm{E}\partial x/D \tag{3.6}$$

Integrating this equation yields the following:

$$\ln(\rho) = \mu\mathrm{E}\partial x/D = \mu V/D \tag{3.7}$$

If mobility and diffusion constants of approximately 10^{-3} cm^2/V sec and 2.6×10^{-6} cm^2/sec can be used for a 0.1M concentration of ions (such as Ca^{++}), in cytoplasmic and interstitial fluids, injury site potentials with magnitudes in excess of 10 mV can meet, or exceed, the conditions required by (3.6) in overcoming diffusion processes producing ionic currents that are directed by the polarity of the injury site voltage and the associated injury site electric field vector. This result is close to the values of endogenous voltages that are produced by various types of injury; including open flesh wounds, fractures, tumor formation, and tuberculous granulomas reported by du Bois-Reymond, Burr, Becker, and Nordenström [32, 36, 39, 40].

At this point, Nordenström's BCEC concepts provide an appropriate model to consider electric field enhanced transport for ions, molecules, and cells that overcomes the response time limitations imposed by simple diffusion models.

Combining Nordenström's BCEC concepts with mathematical expressions for directed transport and nonturbulent flow over nonstreamlined bodies (such as mobile cells), the forces associated with injury site electric fields on negatively charged mobile cells are sufficient to overcome viscous friction and attract immune system cells (white blood cells) to the injury site. The cellular transport times, under the influence of injury site electric fields, are more than 1,000 times faster than the transport times associated with conventional diffusion processes. For example, using Coulomb's law and the nonstreamlined, nonturbulent flow model, the force (F) produced by a 20-μm diameter white blood cell (with an average surface charge density of -0.2 C/m^2 in an interstitial fluid medium) can be related to the force associated with fluid viscosity of the moving cell. Assuming no acceleration,

$$F = q\mathrm{E} = \eta\left(v/d\right)A \tag{3.8}$$

where A is the cross-sectional area of the cell perpendicular to the direction of travel, v is the velocity of the cell, d is the boundary layer thickness, and η represents viscosity.

For nonturbulent flow, the boundary layer thickness can be estimated at 0.03 times the radius of the moving body [38, 41]. If a 20-μm diameter white blood cell with a spherical shape is assumed to be traveling in an interstitial fluid medium with a viscosity coefficient of 10^{-3} kg/ms, an injury potential of 30 mV, a d value of 0.3 μm, and a distance to the injury site of 0.2 cm, the resulting electric field assisted velocity of approximately 0.2 cm/sec allows the cell to be immediately directed and reach the injury site in approximately 2 seconds. This transport time is within the range of observed immune system response times, and is much faster than the transport times associated with simple diffusion.

The relevance, relative consistency, and wide application of Nordenström's BCEC theory are strong indicators that BCEC pathways represent a complementary evolutionary step with biologically closed fluid circuits providing fast transport and precision in the delivery of nutrients, metabolites, and immune system components to specific locations in living systems.

BCEC concepts are not limited to organ-tissue applications. Certain cell membrane receptors, along with their associated electron transfer and phosphorylation pathways, can be thought of as BCEC pathways at the cellular-molecular level. BCEC concepts can also be applied toward energy circulation and metabolism in animals and plants, oxidation-reduction mechanisms, electron transport in the cellular respiratory chain activity of the mitochondria, and photo-phosphorylation activities in plants. Recent research activities involving electron and proton transport mechanisms (including drift and tunneling currents) in proteins and nucleic acids [42–44] indicate that BCEC concepts can also be applicable at the molecular-atomic level.

3.6 Becker's Theories and the "D" Word

Dr. Robert Becker's work and theories are highly complementary with Dr. Björn Nordenström's work and theories. Both men proposed closed loop systems to explain the contribution of certain electrical and electrochemical processes in the body. Generally, the electrical voltages and currents they describe are essentially dc, or voltages and currents that change slowly with time. Nordenström's injury pathways often involve the combination of blood vessels, skin, and nervous system tissue. His regulatory pathways include multiple organs, blood vessels, and nervous system tissue. Becker's injury pathways and regulatory pathways often involve similar vascular and nerve components, and similar tissues and organs. However, in many situations involving injury, the primary component of electrical current is different for Nordenström and Becker. With respect to injury or malignancy, Nordenström's theories and models involve ionic current and variations in ionic flow associated with the injured or diseased area. On the other hand, when discussing injury, Becker's theories and models often involve currents that are made up of mobile electrons associated with unique pathways that include skin, bone, and perineural cells (ependyma in brain and spinal cord cavity, glia of the brain and spinal cord, and Schwann cells that surround nerve fiber).

In Becker's research activities involving amputation and regeneration of limbs in salamanders, the repair of bone fractures in frogs, and injuries in mammals, the injury and healing currents involve the flow of electrons over pathways that are semiconducting. But, at a great cost to his own career, Becker pushed his research efforts well beyond the wildest dreams of biomedicine by addressing

a concept that violated cell biology and medical dogma. That concept involves cell de-differentiation (the "D" word).

Living systems are born, they grow, and they die. It is sometimes difficult to imagine how one of the basic components of living systems (the cell) can revert back to its primitive, embryonic, or immature form and essentially be reborn again. It is also difficult to imagine, if the cell is diseased (for instance, malignant), how it can de-differentiate from the diseased state back to its primitive form, and then redifferentiate as a normal healthy cell. But Becker's work and the work of many others indicate that this is just what happens, and it can happen with a chemical or electrical stimulus. Becker states that immature red blood cells, fibroblasts, and white blood cells can de-differentiate when they are stimulated with very low levels of electric current [32, 33].

In Walter's book, *Options* (1992), some experiments with vitamins are discussed. Vitamin E appears to influence processes that inhibit the growth or proliferation of certain cancer cells, and (sometimes) some of the cancer cells appear to "revert" back to a normal cell [45].

From the standpoint of morphology, murine lymphoma (EL-4) cells appear to undergo reversion when irradiated by pulsed near-ultraviolet laser light at 337.1-nm wavelengths [46]. The irradiated murine EL-4 cell reversion resulted in their return to a morphology resembling lymphoid dendritic cells (LDCs) that are associated with normal mouse spleen cells. Laser light can also promote reversion within the mitotic cycle. As described in [47], irradiation of PTK (female kangaroo kidney) cells with an argon laser resulted in mitotic blockage and mitotic reversion to early prophase.

In a special edition of *Science*, entitled "Frontiers in Medicine" [48], various aspects of limb and tissue regeneration in amphibians, and liver regeneration, wound healing, and skin regeneration in humans were discussed. It is interesting to note that one paper attributes the activity of differentiated marrow stromal cells (MSCs) as the basic resource for nonhematopoietic tissue (healing bone, joint, muscle, and so forth). Another paper discusses skin regeneration almost purely from an enzyme-cytokine-cell differentiation standpoint. However, the last paper openly discusses cell dedifferentiation involving the ability of cultured pigmented epithelial cells of the iris or retina to chemically de-differentiate and transdifferentiate into lens cells in amphibians and humans. In this case, cytokines are discussed as the promoters of the dedifferentiation process.

It was strange to see the words "Frontiers in Medicine" on the feature page of this series of papers in *Science* on regeneration, differentiation, and dedifferentiation. These papers were interesting. But associating them with a medical frontier is somewhat misleading when one realizes that they appeared 30 years after Dr. Robert Becker published his paper on cell dedifferentiation in the *Transactions of the New York Academy of Sciences* [49] and 7 to 12 years after

Becker published his books [32, 33] which provide details of his work on cell dedifferentiation and regeneration. There was no mention of Becker's work in the special edition of *Science*. By ignoring Becker, this scientific journal and the authors of the papers disregarded a significant part of their scientific roots.

In 1997, while my former wife and I were organizing the 1997 Fourth International Symposium on Biologically Closed Electric Circuits (Minneapolis, MN), I sent some material to Dr. Becker concerning his theories and suggestions that, under a limited set of conditions, certain mammalian red blood cells could be dedifferentiated. I received a letter from Dr. Becker, indicating that he never implied mammalian red blood cells could be dedifferentiated. I wrote back, and I asked him to please read the middle of page 200 of his book, *The Body Electric*. I asked him to review what he wrote about immature erythrocytes as members of the mammalian cell candidate population for possible dedifferentiation. Later, I received a nice short letter from him thanking me for my comments. Becker's views are so powerful, innovative, and revolutionary that there are times when he probably had difficulties keeping everything straight himself. But no matter, I had (and still have) a lot of faith in Becker's work and many of his conclusions. I firmly believe that Becker was right, and that new knowledge in cell biology will verify his findings in ways that he may not have imagined when starting out on his journey. One must be aware that supporting and verifying Becker's results and theories can produce very emotional responses in the field of cell biology.

In September 2004, I gave a symposium to a cell biology research group in a medical school. I displayed a series of scanning electron microscope micrographs of allegedly dedifferentiating red blood cells (supposedly, they were immature red blood cells) that had been stimulated with 1-μA currents for a time period of approximately 6 to 16 hours. When I started discussing what those micrographs were implying, with respect to electrically induced cell dedifferentiation, a number of the cell biologists attending were enraged. Several of the attendees left in disgust. They asked, "How can a cell, with a nonfunctioning nucleus, or no nucleus at all, dedifferentiate?" They added, before storming out of the room, "What Becker, you, and the rest of the heretics can't seem to understand is that this phenomena is simply a morphological change in the cell due to an electrically induced change in the cytoskeleton!"

I held my ground, which infuriated them to higher levels. But I knew that I was just experiencing the hysteria of dogma. I have seen chemically and electrically induced cytoskeletal change. With respect to a cytoskeletal change process, the morphology of each cell undergoing change is never as uniform, and not as well sequenced, as the cell changes I was observing. Each morphological variation that I observed matched perfectly with the electrically induced cell dedifferentiation morphology that Becker describes in his papers and book [32, 49]. I was tempted to give them my second answer. But I decided not to bring it

up. My hour-long presentation was almost over, and I did not want to get them more agitated. Also, I didn't have a dagger to defend myself.

My second answer would have been even more shocking to them than the information I had already presented. At that time, I was somewhat aware that the accepted dogma concerning cell structure and the properties and function of various cell components was probably dead wrong. At great cost to his career, Gilbert Ling had introduced his findings concerning the gel structure and characteristics of cells [50]. Ling studied the interaction between water and protein surfaces, and he evaluated a number of biochemical reactions that were sodium pump dependent. He came to the conclusion that the sodium pump hypothesis was incorrect, and that sodium pumping associated with the cell membrane was definitely not the primary control source for the maintenance of ionic concentration differences between the outside and inside of the cell. From his work, and the work of others, the cytoplasm has been described as a gel, with the capability to make significant changes in cytoplasmic water content and cell volume [25]. If the cell is essentially a gel, I knew that some forms of "apparent" dedifferentiation might not need participation from an intact nucleus to change the cell structure back to a primitive or embryonic form. Becker was 30 years ahead of everyone on this particular issue.

Oschman [51] has written one of the clearest descriptions of Becker's proposed system of healing. He describes how the perineural system (involving cells that surround every nerve fiber) is part of a communication/control system for a wide variety of tissues and organs that use direct current (or currents that change very slowly over time) as the primary communication/control signal. An injury current originates from the injury site and alerts the central nervous system concerning the seriousness of the injury and its location. Electric fields associated with the conduction pathway near the wound site attract mobile cells (white blood cells, fibroblasts, and so forth) to assist in the healing process. In the next paragraph, what Oschman describes provides much food for thought. He states that other tissues in the body are surrounded by continuous layers of connective tissue. The vascular system is surrounded with perivascular connective tissue; the lymphatic system with perilymphatic connective tissue; the muscular system with myofascia; the bones with the periosteum. Oschman indicates that the current of injury may not be confined to skin, but may be a general property of the epithelial cell layers. In this case, an injury current can occur in any tissue (epidermal, vascular, muscular, nerve, or bone) that is injured.

If some or all of these continuous layers of connective tissue are semiconducting, Oschman may be describing a fairly complete large-scale version of the dc injury sensing and injury healing communication/control system that Becker has proposed. What is even more exciting is that Oschman may have described the connective tissue system in a way that allows Nordenström's proposed BCEC systems and Becker's proposed dc or low-frequency analog

communication/control system to operate together in series and parallel circuit arrangements. For instance, in Nordenström's BCEC system, ionic currents could be flowing in the vascular-interstitial system. Becker's system involving electron flow could also function, in parallel at the same time, in semiconducting peri-connective tissue associated with the vascular system, nervous system, lymphatic system, bone, muscle, and inner layers of skin. It is a neat package. Their combined theories and models provide an improved combination of interconnected electrically and electrochemically driven subsystems to explain many processes in physiology, immunology, and endocrinology.

Leaning a bit toward Becker, any injury signal directed toward the central nervous system could involve the flow of electrons in the semiconducting cells of the perineural system, specific regions of the central nervous system, and possibly perivascular cells in the vascular system. From the standpoint of healing processes, injury currents or healing currents could involve electron flow, ion flow, or both, depending upon the type and scale of injury or tissue disruption that is being addressed. Also, for wounds and tumors, the combination of Nordenström's BCEC systems and Becker's peri-connective tissue systems, operating in parallel, would provide a set of structures where large pH gradients over short distances can exist.

From these pH gradients, endogenous voltages of 30 mV can produce endogenous ionic healing currents of 30 μA. Electron currents (for sensing, healing, and control), at or above 10 pA, could also be produced by the semiconducting peri-connective tissue systems operating in series and parallel with various BCEC systems. The electron currents would depend upon the size and number of parallel peri-connective structures affected. In this case, relatively large BCEC ionic currents could be encouraging a variety of near-term healing processes. The smaller peri-connective tissue electron currents could be associated with sensing, control, cell dedifferentiation, and long-term tissue/organ regeneration processes. Becker has indicated that the current range of 200 to 700 pA seems to be the best for cell dedifferentiation in red blood cells during the process of fracture healing in certain amphibians [32]. Becker's preliminary results, using small batteries and nerve relocation in mammals, seem to indicate that the required current levels for cell dedifferentiation, redifferentiation, and regeneration in mammals may be at least an order of magnitude higher than the current levels required for amphibians.

In 2006, Alle and Geiger published a paper in *Science* that described combined analog and action potential (AP) coding in hippocampal fibers [52]. Using direct patch clamp recordings, they show that nerve axons in the brain transmit analog signals. They state that AP coding is less efficient than analog coding. The complementary aspects of AP and analog encoding in the mammalian cortex, for information transmission, is in close agreement with Becker's proposed model.

3.7 Ion Transport and Electron Transport in Healing and Regulation

Both Nordenström and Becker have presented results showing a slowly time-varying injury potential as the healing process progresses. However, Nordenström's time-varying injury potentials and Becker's time-varying injury potentials are due to different electrical or electrochemical processes. Considering Nordenström's BCEC system for a mammalian tumor, the initial positive polarity-to-negative polarity variation associated with the tumor site potential [see Figure 3.7(c)] is due to out-migration of the higher mobility hydrogen ions from the center regions of the tumor. Those remaining are the larger slower moving phosphate, chlorine, and other ions.

In his work with amphibians, Becker shows a similar polarity variation (from positive to negative) at the wound site of a salamander that has undergone limb amputation. But Becker's injury site polarity reversals are not the same as Nordenström's tumor site polarity reversals. In Becker's case, the polarity variation is due to the initial dominance of an injury current involving the flow of electrons, and the subsequent increase of current in the opposite direction that is associated with healing and regeneration. Becker has shown how this process occurs in mammals. He explains how it relates to the regeneration process observed with very young children who have had an accident resulting in the amputation of a fingertip.

Together, Nordenström and Becker have provided a set of theories and structures with improvements that overcome some of the limitations that affect conventional models and analytical tools associated with wound healing, cancer treatment, fracture healing, and so on. Their theories may not be perfect, but both of these men developed therapeutic techniques and protocols from their theories, and they have provided valuable insights that offer answers where conventional models fail.

Had these two men received the support and encouragement that they deserved and needed, their work would have enhanced the quality of life and survivability for many people who have or have had severe health problems including cancer, hemangioma, fractures that would not heal, and severe wounds. Patients have died of cancer, lost limbs or lost function, and have suffered needless pain and financial stress simply because the work of these two men has not been incorporated into the mainstream of medical practice. Nordenström's and Becker's colleagues must take the Hippocratic Oath seriously, and stop treating it as if it were a hypocrite oath. There are not enough Nordenströms, Lings and Beckers in this world. And the work they do and results they provide should be appreciated and treated like the life-saving and life-enhancing golden treasures that they really are.

3.8 Impact on Electrotherapeutic Device Design

From an electrotherapeutic device design standpoint, one of the most dominant themes in the combined work of Nordenström and Becker involves the importance of the application of direct current or currents that vary slowly with time. All too often, electrotherapeutic devices are focused on protocols involving the application of different frequencies over specific time intervals. However, for almost 200 years, various publications reporting results of electrotherapeutic techniques in wound healing, treatment of visual disease, treatment of fractures, and cancer therapy provide extensive support for the importance of an appropriately applied dc component in the electrotherapeutic device output waveform. Although there is some variability in the endogenous currents of injury and healing, these variations often occur over periods of many hours or several days. Without the benefit of direct current over a specific time frame, or at least a significant average current associated with each phase of the output signal, many electrotherapeutic devices are being utilized in a nonoptimum or ineffective manner.

Many of the mechanisms Becker describes, which are associated with regeneration and cell dedifferentiation, involve direct current flow. And Becker often makes cautionary statements concerning the use of high levels of therapeutic current and voltage. One of the impacts on design that Becker has provided is to recognize that "less is often better." The results of our own research activities indicate that Becker has a point, especially when applying electrotherapy to highly sensitive organs such as the eye.

In the design of many electrotherapeutic protocols, the chosen waveform often involves a biphase or bipolar configuration "to avoid potential damaging polarization effects on cells." However, approximately 200 years of electrotherapy results in the treatment of wounds, visual disease, and cancer strongly indicate that this particular waveform design dogma may be incorrect for a number of health problems. In many therapeutic applications, interconnected cells in tissue appear to respond and repair very well with dc stimulation or with monopolar signals that have a significant dc component. In fact, in some organ and tissue structures, rectification of the waveform (where the flow of current has a preferred direction) occurs under the influence of various biological structures.

One of the reasons that direct currents or slowly varying currents are important in electrotherapy is that a significant part of the process of healing by endogenous or exogenous electric currents involves the electro-osmotic flow of a fluid solvent (i.e., water) over relatively long distances. This can be a slow process and requires a relatively constant endogenous or exogenous electric field and electric current.

Also, from Chapter 2, as various calculations have clearly shown, mobile ion, molecule, and white blood cell velocities of 0.4 μm/sec to 100 mm/sec, over

distances as short as a few tenths of a centimeter, would require the assistance of fairly constant (dc) or slowly varying applied voltages.

3.9 Summary

If Western medicine wishes to make any further large-scale advances in health maintenance, longevity with quality, and highly effective therapeutic alternatives, the "body electric" must be rigorously incorporated into medical dogma and education. This means that physicians and health care practitioners will have to understand physics just as well as they know (or memorized) their chemistry. There can be no short cuts or end runs around this requirement. As this book is being written, there are certain diseases and health problems that have no effective treatment option other than electrotherapy or magnetotherapy. The response of the body to electrical and magnetic stimulants is, at times, awe-inspiring. The results achieved with electrotherapy and magnetotherapy demand attention.

The primary goal of this chapter is to convince the reader that biological systems regulate, metabolize, heal, and grow based on many facets of their unique electrical properties and characteristics. Biological structure and function are heavily influenced by electrical and electrochemical properties of cells, tissues, and organs. We can almost draw a map from the food we eat and the oxygen we inhale to the electrical activities and responses associated with cells, tissues, and organs. Some of the exercises in Chapters 1 and 2 and this chapter provide parts of that map. These exercise problems show that, if we have information concerning the intake of nourishment in calories, we can estimate oxygen intake requirements, current densities required by a certain percentage of cells to maintain cellular metabolic activity, energy and power, heat transfer requirements, and organ/body temperature regulation. Knowing the electrical properties and characteristics of biological systems helps us to understand biochemistry, biophysics, genetics, molecular biology, cell biology, anatomy, physiology, neurology, sensory systems, pulmonary and cardiovascular systems, endocrinology, reproduction, microbiology, and immunology in a more complete and complementary manner.

Based on a simple model at the cellular level, Thomasset provides an interesting and useful model for the electrical impedance characteristics of healthy and diseased tissue. He provides a design tool that helps to predict variations in the impedance of tissues over time. This information can be useful in the design of electrotherapeutic device waveforms, output characteristics, and treatment protocols.

In different ways the work of researchers such as Becker, Nordenström, Alle, and Geiger have shown that information in the central nervous system

(CNS) can involve a form of digital or discrete signal (action potential) coding along with an analog coding component. Becker described the mechanism for CNS analog coding and he paved the way for this dual concept of nervous system information transfer [32, 33, 51]. As more and more neuroscience research describes the various features and locations of the analog signaling components and pathways, this information will have a major effect on neurology in the coming years.

Exercises

1. Are there mechanical or fluid system analogs for Nordenström's BCEC concept?
2. Many biomedical textbooks contain statements indicating that conduction electrons travel at the speed of light in metallic conductors and in the human body. (a) Is this possible? Why, or why not? (b) The author claims that conduction electrons in ideal metals have drift velocities that are in the millimeter per second range. But wait! We know that in certain types of semiconductor structures, electron drift velocities can be in the range of 10^4 to 10^6 cm/sec. Also, hot electrons in thin insulating films have relatively high velocities. Explain these discrepancies. Why would conduction electron drift velocities in a metal be so much lower than they often are in thin semiconductor and insulator films? (Yes, electrons can be transported across an insulating film, if the film is thin enough, and if the electric field is high enough.)
3. The relationship between velocity, electric field intensity, and viscosity for a charged particle (spherical shape) in a liquid medium can be obtained from Stoke's law: $q\mathrm{E} = 6\pi\eta v R$, where q is charge, R is the effective hydrodynamic radius of the sphere, η represents viscosity, and v is the particle velocity under the influence of the electric field intensity, E. Equation (3.8) provides an expression for charged white blood cell transport through a fluid medium under the influence of an electric field: $q\mathrm{E} = \eta(v/d)A$. These two mathematical expressions would appear to be associated with the same process. Is there any significant difference between the values that each expression would yield using the same dimensions and conditions? If there is a difference, provide an explanation.
4. (a) What is the ion current in a single ion channel? How many ions are involved? (b) How many ion channels would a typical cell membrane

have? (c) Can you determine the total current flow across the membrane due to ion channel currents?

5. Review some of the literature concerning distances, energies, and potentials associated with electron and proton tunneling through energy barriers. For energies up to 1 eV, what are the tunneling distances for electrons and protons?

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4

Electrotherapy and Magnetotherapy Comparisons

4.1 Magnetic Field Properties

Electric, magnetic, and electromagnetic fields can interact with many different kinds of particles and structures including electrons, ions, atoms, molecules, cells, tissues, and organs, resulting in a wide range of effects (both desirable and undesirable) in biological systems. Magnetic fields can alter bond angles of large paramagnetic molecules, changing the way the molecules bond and chemically react with other substances.

Considering magnetotherapeutic applications, static and time-varying magnetic fields can produce short-term or long-term therapeutic benefits. There are basic differences in the way magnetic fields interact with biological system components compared with electric field interactions. An electric field can impose a force on an initially motionless charged particle, producing motion or changes in location and energy state. However, if a magnetic field is to have an effect on the trajectory, location, or energy state of a charged particle, either the charged particle has to be in motion (moving linearly as shown in Figure 4.1, orbiting, spinning, oscillating, and so on), or the magnetic field must be changing with respect to time. Assuming normal conditions, a static magnetic field will not change the position (or energy state) of a completely motionless, nonspinning and nonvibrating charged particle.

Certain substances have their own inherent magnetic properties due to the unique structural components of the material. In this case, when the material is magnetized, the magnetic field lines are modeled in such a way as they appear to originate from one end of the material (north magnetic pole) and terminate on

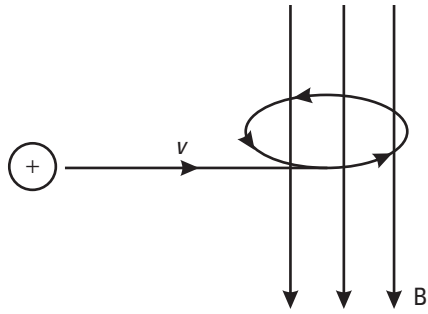


Figure 4.1 Trajectory of a charged particle in a magnetic field. *B* represents magnetic flux density in Webers per square meter, Tesla, or Gauss.

the other (south magnetic pole). However, magnetic field lines do not actually originate at one end of the material structure and terminate on the other, as electric field lines are modeled. The conceptual magnetic model that is often employed involves a set of magnetic field lines that follow a continuous and closed pathway within and around the material.

Magnetic fields can surround the conductive pathway of a material that does not exhibit magnetic properties of its own. In Chapter 2, a number of expressions indicated the relationship between an electric field, E, and a resulting current, *I*, or current density, *J*. The current can involve the transport of ions or electrons:

$$J = I/A = \sigma \mathrm{E} \tag{4.1}$$

If we consider ion flow in a restricted space, or electron flow in a wire, Ampere's circuital law yields a magnetic field intensity, *H* (in Amp-turns/meter), that is a function of the ion or electron current, *I*, (in Amps) and the circumference associated with a specified distance, *r*, from the center of the conductor (as shown in Figure 4.2):

$$H = I/2\pi r = (\sigma \mathrm{E})\, A/2\pi r \tag{4.2}$$

The magnetic permeability, $\mu_R \mu_O$, provides a relationship between the magnetic field intensity, *H* (in Amp-turns/m), to magnetic flux density, *B* (in Webers/m^2), Tesla or Gauss:

$$B = (\mu_R \mu_O) H \tag{4.3}$$

From the above expressions, it is clear that there is a close relationship between electric fields, current, and magnetic fields. For any conductive

From amperes circuital law and magnetic flux density

$$H_\varnothing = \frac{I}{2\pi r} \quad \left(\frac{A \cdot t}{m}\right)$$

$$\vec{B} = \mu_d \mu_r \vec{H} \quad \left(\frac{Wb}{m^2}\right)$$

Charged particles in motion produce magnetic fields.

Figure 4.2 Magnetic field intensity, *H*, surrounding a current carrying conductor, at a distance, *r*, from the center of the conductor, showing the relationship between various parameters in Ampere's circuital law.

pathway that has current flowing through it, a magnetic field will be present around the pathway and its intensity will be proportional to the magnitude of the current.

4.2 Effects of Magnetic Fields on Biological Systems

The instantaneous energy associated with a magnetic field, W_M, can be expressed as a function of the magnetic flux density, *B*, volume, *Vol*, and the magnetic permeability, $\mu_R \mu_O$:

$$W_M = (1/2)(1/\mu_R \mu_O)|B^2|(\text{Vol}) \tag{4.4}$$

Considering the volume, *Vol*, of a 20-μm mammalian cell, the range of energies associated with 20- to 400-mT magnetic fields would be approximately 1.3×10^{-12} J to 0.51×10^{-9} J. Energy levels of 10^{-9} J (and above) may be large enough to have small or subtle effects on weak chemical bonds, ligand-receptor interfaces, transport mechanisms, and biochemical responses in mammalian cells or cell components (such as cell membrane receptors, ion channels, and transporters) [1]. Time-varying magnetic fields with magnetic flux densities of 1 to 400 mT have shown evidence of influencing in vitro cell proliferation, tumor growth inhibition and apoptosis [2, 3]. Magnetic fields at lower flux densities appear to have an effect on cytokine receptor gene expression, expression of oncoproteins, and DNA synthesis [4–6].

Experimental evidence indicates that mT magnetic field flux densities can have an influence on biological systems. However, blind application of instantaneous energy relationships, such as (4.4), and other energetic arguments, often fail to support observed biological impacts or the applicability of much lower level field strengths (electric or magnetic). Other fundamental relationships can be used to predict and quantify biological impacts at very low magnetic field intensity and flux density values when basic energy equations are not adequate, or are misapplied.

Ion cyclotron resonance (ICR) and *ion paramagnetic resonance* (IPR) have been proposed as magnetic field dependent mechanisms that could influence the transport of charged entities across cell membrane ion channels for low-level magnetic fields in the μT range [7, 8]. There is considerable debate on whether the proposed biologically relevant mechanism is ICR or IPR [9, 10]. Others claim there is no evidence that these mechanisms can influence biological systems [11, 12].

The ICR model, proposed by Liboff (Figure 4.3), can be derived by equating the centrifugal force of an ion in circular motion, with the Lorentz force. In this case, the induced electric field component is assumed to be 0 V/m. The ICR model indicates that biological responses can be predicted based on a relationship involving a resonant frequency, f_{ICR}, to an applied magnetic flux density, B_Z, and a charge, q, to mass, M, ratio for the ion:

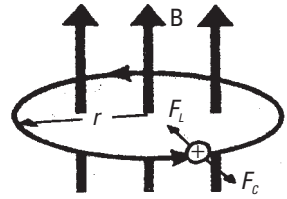
$$f_{ICR} = qB_Z / 2\pi M \tag{4.5}$$

In this model, each ion species has a unique resonant frequency depending upon its charge to mass ratio. For instance, considering a Ca^{++} ion, the charge to mass ratio is 4.29×10^6 C/kg. The resonant frequency value for a 38-μT magnetic flux density, B_Z, would be 26 Hz. This value agrees with experimental data provided by Liboff.

There are a number of mathematical relationships, contained within Maxwell's equations, supporting the possibility that extremely low-level magnetic fields can have biological effects and therapeutic benefits. One of Maxwell's equations indicates that a time-varying magnetic field in the y direction induces an electric field in the x-direction (where the two fields are perpendicular to each other), and the electric field will change in the z-direction, as shown in (4.6).

$$\partial B_Y / \partial t = -\partial \mathrm{E}_X / \partial_Z \tag{4.6}$$

Equation (4.6) and its integral form (often referred to as Faraday's law) have implications that can be substantiated experimentally in living systems. For instance, [2] discusses how the proliferation of mouse fibroblasts and human



Centrifugal force (F_c) = Lorentz force (F_L),
$m(\omega_{icr})^2 = q(E + v \times B)$,
Assume: $E = 0$ and $v = r\omega_{icr}$,
$m(\omega_{icr})^2 = q(r\omega_{icr}B)$.
Therefore, $f_{icr} = (1/2\pi)(q/m)(B)$.

Figure 4.3 Ion cyclotron resonance model.

HL-60 leukemia cells can be influenced by the application of a 50-Hz sinusoidal magnetic field with 2.8-mT (peak) magnetic flux densities. The measured electric fields induced by the time-varying magnetic field were 8 to 12 mV/m (peak). The authors maintained that the variations in cell proliferation observed with the application of the magnetic field were actually due to the induced electric field.

From Faraday's law, a relationship can be derived between an electric field around a closed pathway of radius r, E_ϕ, and a magnetic flux density, B_Z, that has a constant magnitude within the area defined by the closed pathway. Using this relationship, the magnitude of E_ϕ is equal to $\omega r B_Z/2$. At 50 Hz, the calculated peak value for E_ϕ, induced by a magnetic field intensity of 2.8-mT peak, is 4.4 mV/m for a radius of 1 cm, which is close to the data shown in [2].

Applications of mathematical relationships, such as (4.6) and Faraday's law, to biological system structures and materials can yield different results when compared with actual measurements. Equation (4.6) may not give accurate values if the biological system is oversimplified and modeled as a homogenous material medium with typical values assumed for dielectric constant, magnetic permeability, and conductivity. However, regardless of any analytical limitations for specific biological structures, (4.6) and Faraday's law provide part of the foundation that can be used to predict the measurable or observable effects that occur when large and small magnetic fields are applied to biological systems.

In a conductive medium or conductive pathway, as implied by (4.1), an induced electric field will produce a current density or current that flows in the same direction as the induced electric field vector.

$$J_X = I_X / A = \sigma_X E_X \tag{4.7}$$

Equations (4.7) and (4.8) show the relationship between a magnetic field and current.

$$B = (\mu_R \mu_O) H = (\mu_R \mu_O) I / 2\pi r \tag{4.8}$$

One might ask: What kind of magnetic field intensities or flux densities could we expect from currents associated with nerve fibers in the central nervous system? Equation (4.8) indicates that a magnetic flux density of approximately 0.1 pT would result for a current of 1 nA, at a distance of 2 mm from the center of the conductive pathway, assuming an infinitely long conductive wire filament model for a nerve fiber. Using an improved model for nerve structures in the CNS, magnetic flux densities of 0.02 pT have been calculated for nerve fiber excitatory postsynaptic potential (EPSP) currents of 1 nA, at distances of approximately 2 mm from the center of the neuronal cell body or soma [13]. Obviously, the results obtained from a simple wire filament model will not give the same results as a model based on a more complex nerve fiber structure and environment. However, the more complex nerve fiber calculations were based on expressions related to (4.8).

We might ask the previous question in reverse: What kind of currents could we induce in nerve fiber with an extremely small (pT) magnetic flux density; and would the induced current be biologically significant? Maxwell's equations provide a simple mathematical expression showing the relationship between a magnetic field intensity, H_X, that is changing in the z-direction with an induced current density, J_Y, that has a direction perpendicular to the magnetic field intensity:

$$\partial H_X / \partial z = J_Y \tag{4.9}$$

We can assume that a set of magnetic coils is placed a few centimeters from the cranium. Using (4.8) along with appropriate values of distance, a low frequency current of 2 μA in the coils can produce a magnetic field intensity of approximately 64-μA turns/m to a value of 46-μA turns/m over a distance of approximately 1 cm near the top layers of brain tissue. The corresponding magnetic flux densities would be 80 and 58 pT, respectively. In this case, according to (4.9), a current density of approximately 1.8 mA/m^2 would be induced in the conductive pathways of the brain by the 18-μA turns/m difference over the 1-cm distance. The resulting current in a 24- to 100-μm nerve fiber would be approximately 0.8 to 14 pA. Therefore, using one of Maxwell's equations, a spatially varying magnetic field that changes from 58 to 80 pT, over a distance of approximately 1 cm, can produce current magnitudes that are fairly close to the 4-pA levels associated with individual acetylcholine (ACh) channels and 50- to 75-pA levels associated with miniature excitatory postsynaptic currents (mEPSC) in hippocampal synapses.

Do these calculations prove that pT magnetic flux densities can influence synaptic currents in nerves and synaptic pathways of the brain and produce a

magnetotherapeutic effect? The answer would have to be no. The calculations, based on Maxwell's equations, do not prove anything. Just because the current magnitudes obtained with Maxwell's equations agree with experimental data, it does not prove that the Maxwell equation mathematical model is correctly applied. However, the results obtained from (4.8) indicate that by using known physiological parameters and nerve fiber dimensions associated with various regions in the brain, several components of Maxwell's equations yield calculated current levels that are close to the actual currents associated with neural components of the brain, including hippocampal synapses. Therefore, the calculations provide some support for the possibility that pT magnetic fields could have some influence on currents associated with neural pathways in the brain.

Even though Maxwell's equations predict current levels for applied pT magnetic fields that are quite close to actual current levels in the brain; how do we rationalize a biological effect for pT magnetic fields when the instantaneous energy levels are many orders of magnitude below the energy levels associated with the weakest chemical bond or the dreaded thermal noise limit? First of all, the word "instantaneous" should give us food for thought. Instantaneous energy concepts are often too limited. A more appropriate energy model might utilize quantum mechanics principles and integration over time, frequency, and space. Nordenström, Becker, and Oschman have provided a few clues or hints in their work that seem to suggest that a quantum mechanics link to an energy model would be more appropriate [14–17]. Limitations that are often attributed to thermal noise levels can be overcome if various integration or summation processes are considered.

Becker provides two essential ingredients in his proposed closed loop negative feedback dc communication-control system involving the brain and the perineural cells (glial cells and Schwann cells). Becker indicates that this system involves very low frequency analog signals (and analog controls) [16]. The perineural cells are associated with many parts of the nervous system and appear to be semiconducting (the first essential ingredient). Also, other protein components of unmylelinated nerve fiber (such as dendrites) contain protein components (such as microtubules) that could exhibit semiconducting properties.

If portions of the nerve fiber protein are semiconducting, we can consider that at certain locations in the conducting pathways of the brain, electrical current involves the flow of electrons over a semiconductor pathway (the second essential ingredient). At this point, we can make some very bold assumptions. If electron flow is involved, an energy relationship can be derived from the Lorentz force and the external force on a charged particle, where h is Planck's constant and f is the magnetotherapeutic signal frequency. The contribution from the induced electric field is assumed to be negligible. Also, we will assume that phase velocity, v_p, is approximately equal to group velocity, v_g, and instantaneous velocity, v_I.

$$W_{LE} = hf \approx (1/11\pi) B v_I L_q \tag{4.10}$$

The details associated with (4.10) will be presented in Chapter 5. For this application, (4.10) assumes charged particles (electrons) in nerve fiber proteins, with site-to-site transfer intervals, L, of 10Å, site-to-site hopping times, τ, of 0.42×10^{-14}, an instantaneous velocity of 2.38 10^5 m/sec (which is approximately a factor of 10 below the Fermi velocity for a typical inorganic semiconductor), a magnetic flux density of 7 pT, and a charge of 1.6×10^{-19} C. With respect to (4.10), a certain range of pT magnetic flux densities, B, yield signal frequency values, f, that are in close agreement with published clinical data obtained for epilepsy and Parkinson's disease patients. These patients were successfully treated by Anninos with pT magnetotherapy [18, 19].

The derivation of (4.10) is interesting, as Chapter 5 will reveal. However, a few comments should be made concerning this strange and somewhat controversial relationship. A number of biophysicists have looked at the expression and stated that the frequency term should be the vibrational mode frequency that is actually associated with thermal excitation, ν, and not the signal frequency, f. After going through the derivation, their criticisms seemed to be correct. I began to have second thoughts. It appeared that my modeling effort, using quantum mechanics, electron wave packets, electron wave numbers, k, free electron momentum, $hk/2\pi$, and so on, was just a desperate and misguided attempt to generate an energy-based design tool for therapeutic protocols involving subtle energies.

By using the thermal vibration mode frequency term, (4.10) is out of balance by a factor of approximately 10^{12}! I was ready to dump the whole idea. It seemed to me that I made the same mistake that others have made by slapping relationships together that were not compatible. I was also embarrassed. Then, I realized that I had (by accident) incorporated something in this model that no one (including me) seemed to notice. The electron momentum and force side of the equation involves continuous processes; the Lorentz force side of the equation involves discrete events over very short time periods. Without realizing it, when I did the initial derivation, I had applied an appropriate averaging ratio, which made the continuous electron momentum expression compatible with the discrete and very short time frame Lorentz force expression.

Another interesting spin on this model could be done if we consider a more macroscopic definition of the charge q. Under certain conditions, a time-varying magnetic field could have a temporary synchronizing effect on groups of vibrating electrons that are lightly coupled and concentrated within small volumes. Small volume segments associated with primary neuron components could be considered as regions where electron excitation by magnetic fields might produce relatively uniform and coordinated responses. Under these

conditions, the charge variable in (4.10) could represent the coordinated or synchronized movement of a large number of charges. This synchronizing effect could occur for the relatively short intervals within hopping time frames, collision time frames or relaxation time frames of approximately 10^{-8} to 10^{-14} seconds. The magnetic field could provide just enough energy to coax many of the "almost-free electrons" into the conduction band. This would enable them to collectively move (or hop) in a coordinated or coherent manner from region to region in a semiconducting protein or nucleic acid, in 10-Å increments, over very short time intervals, under the influence of an applied magnetic field. In this case, the individual charge term, q, would be replaced by a total charge term, Q, obtained by using volume integration.

Well, a number of theories in physics and chemistry have been stretched far enough in order to give some credibility to (4.10). This equation, and some of the assumed parameter values, may or may not be relevant to biological systems or magnetotherapeutic applications. However, Becker's semiconducting dc communication-control system proposal provides an appropriate physical environment for relationships similar to (4.10), and these relationships are very interesting with respect to their implications. Therefore, in Chapter 5, we will take a closer look at equations that appear to have inequality problems, and we will derive (4.10). One might ask, "Why should we care?"

We must care! This is an engineering book. It addresses design and application issues. The engineer must be trained in the arts of problem solving (requiring a large amount of analytical effort) and applications (involving significant design or synthesis components). The engineer uses the fundamentals and tools that math and science provide. Often, the engineer must derive equations and relationships that impact the areas of analysis, design, manufacturing, and applications. The engineer designs components, systems, firmware, and software providing items that do useful work, that heal, that measure, that inform, and that explore. Religion, medicine, physics, and chemistry can hang on to their dogmas if they wish. But engineering does not have this luxury. When engineers have a death grip on dogma and are dedicated to "the way we have always done it," under changing conditions, their bridges and buildings collapse, their dams and levy systems burst, their circuits burn out, their batteries explode, their software crashes, their airplanes break apart in mid-air, their materials undergo unexpected chemical reactions and become toxic, their automobiles tip over, and their patents are invalidated.

Many scientists do not get involved in applications or design. So, they can deny that an unexpected effect or result exists. This often gives them a chance to write a paper that refutes the unexpected effect or result. But engineers have to deal with reality. If an effect or phenomena exists that has a useful application, engineers must construct analytical models and establish design rules for the effect or phenomena and apply those rules. Engineers must develop models and

mathematical relationships that allow them to predict outcomes. These models and relationships can help to develop or evolve the appropriate guidelines to design devices that are useful, reliable, safe, and reasonable with respect to costs and impact on the environment. If an established dogma or model does not provide the appropriate analytical tools for a specific application, design process, or analysis, the engineer must often develop new tools and models to address design and analysis tasks. Engineers cannot simply "blow it off" because "it doesn't fit."

In the case of magnetotherapy, when an engineer sees that a pT magnetic field actually does produce a biological effect and reasonably consistent therapeutic results, the engineer cannot just simply reach for a grab bag of equations that do not support the observation and state, "there is no effect." The engineer cannot engage in denial and ignore valid and verified therapeutic results for patients with Parkinson's disease and non-trauma-induced epilepsy. When a result or effect occurs that is not anticipated or predicted by established analytical tools, rules, and dogma, the engineer has to try to develop new analytical tools and rules that will be useful in design, design optimization, development, manufacturing, and application.

4.3 Magnetotherapy Clinical Studies

Magnetotherapeutic and electrotherapeutic devices can be applied to the same diseases or health problems. Both can be utilized in the treatment of bone fractures [20–22], neurological disease [18, 20, 23], ulcers and connective tissue disease [20, 24], cancer [14, 20, 25–27], and pain [20, 28]. Magnetic fields can produce a number of different effects in organs and tissues. However, unlike their electrotherapeutic counterparts, magnetotherapeutic devices are not simple with respect to structure and operation, and magnetic fields are not easy to measure and monitor directly. The presence of external magnetic fields, metal structures and metal deposits can have a significant effect on the consistency of results achieved with most low-level magnetotherapeutic techniques and protocols. Also, the interaction of magnetic fields with biological systems is often much more difficult to explain to those who do not have a solid background in physics.

Magnetotherapy applications generally do not require the magnetic source to touch the tissue, allowing magnetic fields to be coupled to tissue more effectively. In comparison, electrotherapeutic devices often require physical contact between a source electrode and tissue. In this case, a significant amount of the applied voltage is lost at the electrode-tissue interface.

The use of magnetic materials and devices for therapeutic and/or rejuvenation purposes dates back to the ancient Greeks, Chinese, and Egyptians. In the

early 1500s, Paracelsus used magnets in an attempt to treat epilepsy, gastrointestinal disease, and hemorrhage problems. In the early 1600s, William Gilbert treated strangulated hernias with magnets [29].

The therapeutic effects of magnetotherapy can be quite dramatic. Figure 4.4 shows before-and-after results for two cancer patients with significant bone deterioration due to breast cancer metastasis. Treatments were administered by Dr. Demetrio Sodi Pallares (deceased) of San Geronimo (Mexico City), Mexico. The magnetotherapeutic protocol for these two patients involved the application of a time-varying 60-Hz magnetic field with a magnetic flux density of approximately 20 mT [1, 20]. The patients received pulsed magnetic field

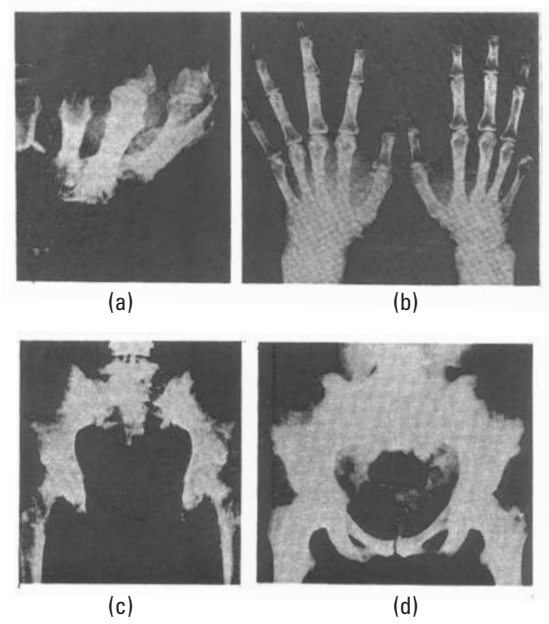


Figure 4.4 (a) X-ray images of high level of deformation and bone destruction in the hand and wrist for a breast cancer patient where the cancer metastasized to different parts of her body. (b) X-ray image of patient's hands after three months of combined pulsed magnetotherapy treatment and a low-sodium/high-potassium diet. Four months later, the bone deformation and damage that was evident on previous x-ray images was no longer detectable. (c) X-ray image of severe destruction of pelvic bones for a breast cancer patient with advanced pelvic metastasis. (d) After showing no response to chemotherapy, Dr. Sodi Pallares treated her with pulsed magnetotherapy, polarizing solution treatments, and a low sodium-high potassium diet. After 6 months of treatment, the signs of osteolysis are gone and the patients pubic bones and pubic arch are well defined. (All photographs courtesy of Dr. Demetrio Sodi Pallares, San Geronimo, Mexico. Also see [1, 30]. Permission also granted by IABC Foundation.)

therapy for 4 to 5 hours each day, were placed on a low-sodium/high-potassium diet, and received the Sodi Pallares polarizing solutions five times per week.

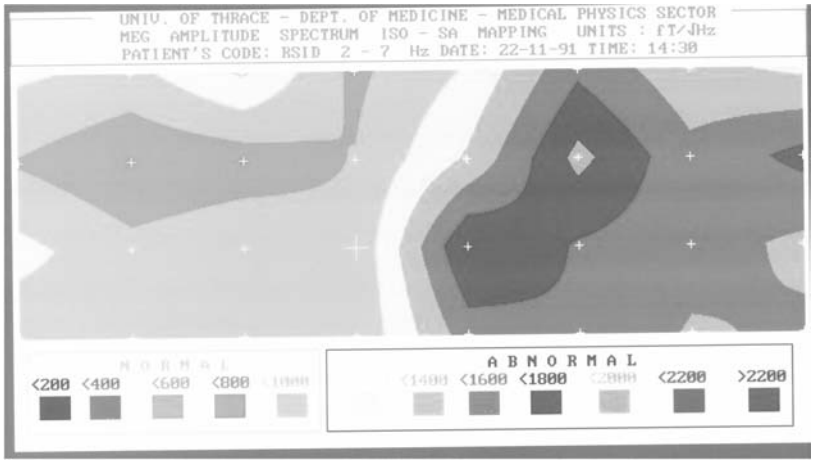
Patients suffering from Parkinson's disease and nontrauma-induced epilepsy [18, 19] have been treated with picoTesla magnetotherapy (pT-MT) for more than 20 years. Hundreds of patients have been treated with this unique and safe technique by Dr. Photios Anninos at the University of Thrace, Department of Medicine, Medical Physics Sector, Alexandroupolis, Greece. In Figure 4.5, Dr Anninos is shown adjusting a 122-channel liquid helium cooled Superconducting Quantum Interference Device (SQUID, operating at a liquid helium temperature of 4°K) to obtain magnetoencephalogram (MEG) data for a Parkinson's disease patient who has just been treated with pT-MT. This system provides the capability for whole-brain real-time monitoring and recording. Figure 4.6 shows a Parkinson's patient wearing a pT-MT helmet, containing magnetic field coils linked to a low-level current signal source. The patient is treated with pT magnetic flux densities at frequencies that are close to the patient's alpha rhythm frequency (8 to 13 Hz). The alpha rhythm frequency for each patient can be determined by MEG measurements with the SQUID (using a Fourier statistical analysis of the MEG values) [19] or with an electroencephalogram (EEG) recording.

Figure 4.5 Patient being treated for Parkinson's disease by Dr. Photios Anninos. Dr. Anninos is shown adjusting a liquid helium cooled Superconducting Quantum Interference Device to obtain magnetoencephalogram data. (Courtesy of Dr. Photios Anninos, University of Thrace, Department of Medicine, Medical Physics Sector, Alexandroupolis, Greece. Permission given by IABC Foundation.)

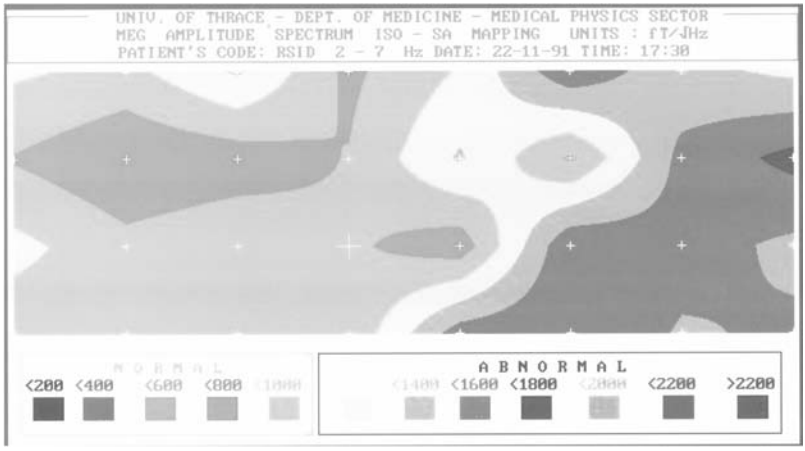
Figure 4.6 Patient being treated for Parkinson's disease with a picoTesla magnetotherapy unit encased inside a helmet. (Courtesy of Dr. Photios Anninos, University of Thrace, Department of Medicine, Medical Physics Sector, Alexandroupolis, Greece. Permission given by IABC Foundation.)

Parkinson's disease appears to involve a variety of health problems with certain subdivisions. Some patients can acquire a Parkinson's disease condition following a viral infection, trauma, or after atherosclerotic complications. Others may have a Parkinson's condition induced by a medication or exposure to a neurotoxic heavy metal contaminant (oxidative stress can occur with high levels of manganese or iron). There are some genetic predisposition and/or neurotransmitter deficiency factors. Also, many Parkinson's patients have a weakness for sweets.

Parkinson's disease can exhibit characteristics similar to those associated with other neurological disorders such as benign essential tremor, Wilson's disease (inherited defect in excretion of copper by the liver), Huntington's disease (inherited single faulty gene in chromosome #4), or Alzheimer's disease (genetic factors, exposure to contaminants, history of head trauma, neurotransmitter or hormonal deficiencies, exposure to heavy metal toxins including aluminum and mercury). MEG data taken for a Parkinson's disease patient are shown in Figure 4.7. Figure 4.7(a) shows the MEG data before pT-MT treatment, indicating very abnormal MEG activity in the right half of the photograph. Five hours after



(a)



(b)

Figure 4.7 (a) MEG representing the magnetic field intensities of the left temporal region for a Parkinson's disease patient. The data was obtained just before the patient was treated with pT-MT. Higher magnetic field intensities occur with the disease. The darker regions represent the areas of highest magnetic field intensity. (b) MEG for the same patient 5 hours after initial treatment. Notice, the MEG shows a decrease in magnetic field intensity after pT-MT treatment. (Courtesy of Dr. Photios Anninos, University of Thrace, Department of Medicine, Medical Physics Sector, Alexandroupolis, Greece. Also see [1].)

the initial pT-MT treatment, Figure 4.7(b) shows significant reduction of abnormal MEG activity at the right-half portion. During this time, the patient's tremors decreased noticeably. The patient reported a reduction in muscular

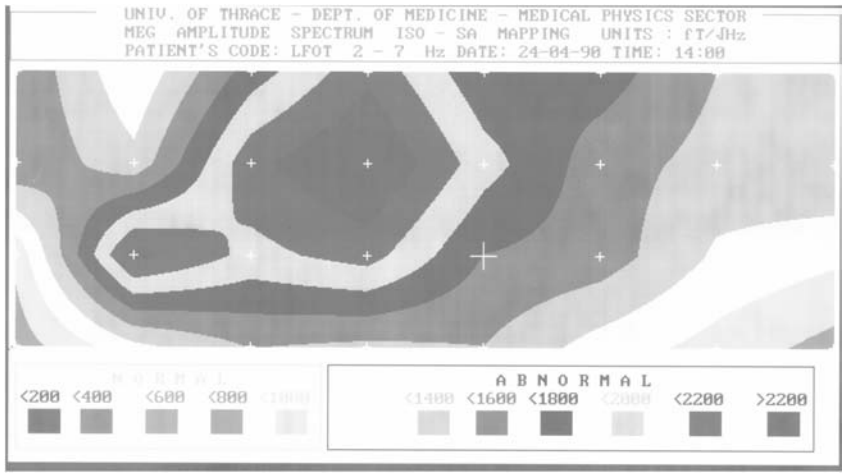
aches along with coordination and visiospatial improvements. Many patients report a significant reduction in feelings of depression after two treatments. However, stress and dietary mismanagement can negatively impact the treatment results. Also, some patients with very noticeable tremors do not seem to respond initially. Their MEG data may not show much improvement. But after continuing their home treatments, significant improvements begin to occur long after their first treatment.

Approximately 75% of Parkinson's disease patients respond to pT-MT, and treatment results can vary considerably. However, many Parkinson's disease patients treated with pT-MT show significant improvements in reduction of tremors, increased energy, more natural facial expressions, significant speech improvements, better posture and coordination, enhanced mobility (ability to drive a car, dance, or play golf), and improvements in mood and sleep.

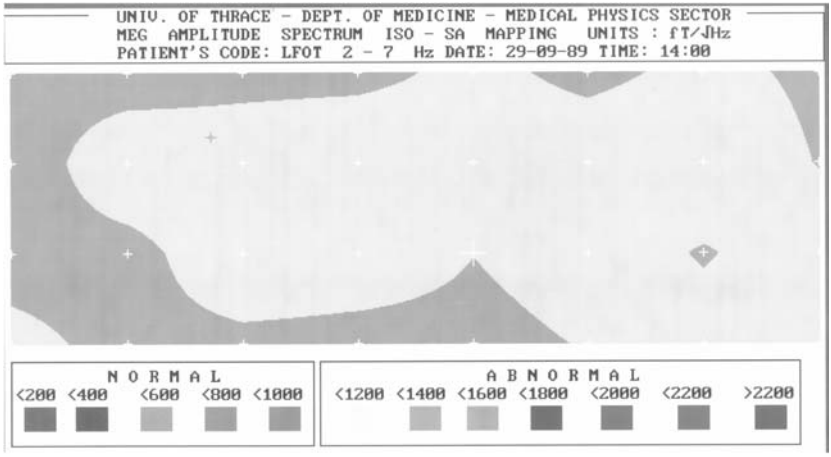
The pT-MT technique has also been useful in treating non-trauma-induced epilepsy. Figure 4.8 shows MEG data of the left temporal region for an epilepsy patient. The pretreatment MEG data [Figure 4.8(a)] shows abnormally high magnetic field intensities in the region afflicted. The post-treatment MEG data [Figure 4.8(b)] shows the MEG data for the same patient after treatment with pT-MT. The magnetic field intensities are significantly lower, and patient seizure activity significantly decreased in severity and frequency with additional pT-MT treatments.

Magnetotherapy appears to be effective for a variety of health problems using magnetic field flux densities exceeding 1T all the way down to pT levels. It would appear that magnetic flux densities close to the 1T level might be influencing polarity and action potential characteristics in the CNS which could have significant influences in wound healing and treating depression. The mT magnetic field flux density level appears to have an influence on chemical bonds, ligand-receptor interfaces, and transport mechanisms for treating cancer, pain, and connective tissue disease. At μT levels, cyclotron resonance phenomena indicate that magnetotherapy may have some influence in ion channel transport mechanisms, which may be useful in cancer therapy and bone fracture repair. At pT levels, magnetotherapy could, in theory, influence pA currents associated with nerve synapses, providing applications in certain nervous system disorders. It appears that as the magnetic field flux density decreases from the mT level to the pT level, the possible biological system interaction mechanisms seem to make a transition from conventional electrodynamics and kinematics (mT level), to cyclotron resonance effects (μT levels), and finally progressing toward subtle energy and quantum effects (pT level).

From a magnetotherapeutic standpoint, interaction mechanisms associated with the higher magnetic field levels would appear to be more suitable for wound healing, connective tissue disease problems and treatment of certain kinds of depression. The mid-range magnetic field levels appear to be more



(a)



(b)

Figure 4.8 (a) MEG data representing the magnetic field intensities of the left temporal region for a nontrauma-induced epilepsy patient. The data was obtained just before the patient was treated with pT-MT. Higher magnetic field intensities occur with the disease. The darker regions represent the areas of highest magnetic field intensity. (b) MEG data for the same patient several hours after treatment. Notice, the MEG shows a significant decrease in magnetic field intensity in the entire region after pT-MT treatment. (Courtesy of Dr. Photios Anninos, University of Thrace, Department of Medicine, Medical Physics Sector, Alexandroupolis, Greece. Also see [1].)

suitable for applications in cancer treatment, disorders in cell signaling pathways, fracture repair, and pain mitigation [20, 27, 29, 31]. The very low-level

magnetic flux density levels appear to be more applicable to certain nervous system disorders such as Parkinson's disease, certain kinds of depression, and nontrauma-induced epilepsy [1, 18, 19].

For magnetotherapeutic applications specific to oncology, the stronger mT fields appear to have more of a direct impact in tumor and cellular structural elements [1]. In this case, chemical bonds could be affected, ligand-receptor interfaces could be distorted, and the transport or motion of ions and electrons could be significantly influenced. Some laboratory results indicate that mT magnetic fields can compromise tumor tissue and the vascular structure of the tumor, induce necrosis in tissues, change cell morphology, enhance natural killer cell activity, induce apoptosis and lytic activity in cells, and produce therapeutically significant pH changes in the tumor [20, 29, 32–36]. The mT magnetic flux densities also appear to have an affect on cellular communication, cell proliferation, cell membrane receptor activity, cytokine receptor expression, oncoprotein expression, cyclic nucleotide, and kinase regulation, DNA structural integrity, DNA binding capabilities, and transcription [2–6, 37–39]. In addition, μT magnetic flux densities appear to have the capability to alter Ca^{2+} transport and binding protein activity [9]. All of these effects could have significant impacts on tumor structure and the morphology and proliferation characteristics of malignant and normal cells [1].

For those of us who are more focused on electrotherapy, we must constantly remind ourselves that every electrotherapeutic current is associated with a magnetic field surrounding the electrical conduction pathway [15, 16, 40, 41]. The resulting magnetic field intensity is proportional to the magnitude of the electric current (Ampere's circuital law). Therefore, when electrotherapeutic devices are applied, we may also be providing a significant magnetotherapeutic component as well [15].

Likewise, in many magnetotherapeutic applications [and as shown in (4.6)], a time-varying magnetic field can induce significant electric fields and currents in tissue and organs [32, 40, 41]. When magnetotherapeutic devices are used in therapeutic applications, an electrotherapeutic component may also be involved.

4.4 Summary

Magnetic fields can interact with many different kinds of charged entities and structures including electrons, ions, atoms, molecules, cells, tissues, and organs, resulting in a wide range of effects in biological systems.

Static and time-varying magnetic fields can produce short-term or long-term therapeutic benefits. There are basic differences in the way magnetic fields interact with biological system components compared with electric field

interactions. If a magnetic field is to have an effect on the trajectory, location, or energy state of a charged particle, either the charged particle has to be in motion (moving linearly, orbiting, spinning, oscillating, and so on), or the magnetic field must be changing with respect to time. Assuming normal conditions, a static magnetic field will not change the position (or energy state) of a completely motionless, nonspinning and nonvibrating charged particle.

Magnetic flux densities close to the 1T level appear to be influencing polarity and action potential characteristics in the CNS, which could have significant influences in wound healing and treating depression. The mT magnetic field flux density level appears to have an influence on chemical bonds, ligand-receptor interfaces, and transport mechanisms, which would be applicable in treating cancer, pain, and connective tissue disease. At μT levels, cyclotron resonance phenomena indicate that magnetotherapy may have some influence in ion channel transport mechanisms, which may be useful in cancer therapy and fracture healing. At pT levels, magnetotherapy could, in theory, influence pA currents associated with nerve synapses with applications in certain nervous system disorders.

As the magnetic field flux density decreases from the mT level to the pT level, the possible biological system interaction mechanisms appear to make a transition from conventional electrodynamics and kinematics (mT level), to cyclotron resonance effects (μT levels), and finally progressing toward subtle energy and quantum effects (pT level).

Ampere's circuital law indicates that when electrotherapeutic devices are applied, we may also be providing a magnetotherapeutic effect as well. Likewise, in many magnetotherapeutic applications a time-varying magnetic field can induce significant electric fields and currents in tissue and organs. When magnetotherapeutic devices are used in therapeutic applications, several components of Maxwell's equations indicate that an additional electrotherapeutic effect may also be involved.

Exercises

1. Hydrogen, ammonia, bismuth, beryllium, silicon, germanium, phosphorous, sulfur, chlorine, the inert gases, and so on are all diamagnetic. Oxygen, tin, aluminum, copper sulfate, lithium, manganese, tantalum, platinum, and so on are all paramagnetic. What kind of behavior does a paramagnetic material exhibit in the presence of a magnetic field? What kind of behavior does a diamagnetic material exhibit in the presence of a magnetic field? Why are both effects so weak?

2. Inorganic crystals of magnetite (Fe_3O_4) have been found in bacteria, in tissues of the human brain, and in a considerable number of cancer cells. What is the purpose of magnetite in bacteria, brain cells, and cancer cells? What could be the origin of the magnetite material?
3. Outline the requirements and show a simple block diagram for a system that could obtain a magnetically sensitive image that shows differences in magnetite concentrations between normal and diseased tissue. Outline one of the more expensive design and manufacturing issues associated with this imaging system.
4. If pT magnetic fields can be used to treat Parkinson's disease and nontrauma-induced epilepsy, is there a reason why a 1T magnetic field cannot be used to get a stronger magnetotherapeutic response? Are any systems using 1T magnetic fields employed in magnetotherapeutic applications or diagnostics?
5. Describe how a magnetic field might interact with a strand of DNA. Is the interaction just electromagnetic, or can the magnetic field actually cause a physical distortion of the DNA double helix?
6. Review some of the information on the probable causes of Parkinson's disease and probable causes of nontrauma-induced epilepsy. Describe possible mechanisms for some of the processes and elements involved that enable a pT magnetic field to reverse, or slow down, the process of degeneration in Parkinson's disease. Do the same for nontrauma-induced epilepsy.

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5

Potential Biological Effects of Subtle and Not-So-Subtle Energy Levels

5.1 Introduction

Many research papers have stated that electric and magnetic fields at low intensities or certain frequencies have no effect on biological systems. Part of the problem with this kind of claim is that the conclusions are often based on conventional energy relationships and models that are either incomplete or inappropriately applied. Another conclusion that seems to run amok with certain scientists involves the belief that once instantaneous electromagnetic intensity levels (or average energy levels) drop below the thermal noise level, the signal is drowned out by noise and cannot have a biological impact. If integration, summation, or stochastic resonance processes are involved, this conclusion is often wrong.

Some medical doctors make the bold claim that "electricity has no place in healing or regulation in the human body." If electricity has no place in healing or regulation in the human body, we would have to eliminate the process of conscious thought, cancel out the sympathetic and parasympathetic nervous system, remove the heart (especially the sinoatrial node), remove the renal system and eliminate all wound healing. Furthermore, since many cells in the human body require an ionic current density of approximately 1 mA/cm^2 to maintain their basic metabolic rate, most, if not all, of the cells would have to be removed from the body. Now, all that is left is a very tiny rock and some water. No, wait! We cannot have water. Water is electrically polarized. So we must get rid of the water and leave just the very tiny remnant of solid particulate matter as our life form.

Does all of that seem a little silly? Yes, silly results and conclusions often occur when limited thinking and narrow dogma are applied to any kind of system. Without the appropriate electrical (and, in some cases, magnetic) processes and effects that occur in living systems, microbial, plant, and animal life could not exist and the entire universe would be a very dull and lifeless place.

5.2 Energy Levels Associated with Electric, Magnetic, and Electromagnetic Fields

Equations (5.1) and (5.2) provide an overview of the energy relationships that are associated with electric and magnetic fields. Equation (5.3) shows the impedance relationship involving the electric field and magnetic field components of an electromagnetic wave in free space. The relationship for the energy of an electric field, W_E, is

$$(W_E) = (1/2)\varepsilon_O \varepsilon_R |E^2| \text{Volume} \tag{5.1}$$

and the relationship for the energy of a magnetic field, W_M, is

$$(W_M) = (1/2)(1/\mu_O \mu_R)|B^2| \text{Volume} \tag{5.2}$$

Also, the 377Ω impedance of free space establishes the relationship between the electric field component and the magnetic field component for the electromagnetic field:

$$\eta = 377\Omega = E/H = \mu_O \mu_R (E/B) \tag{5.3}$$

where half of the energy associated with the electromagnetic wave is contributed by the electric field component and the other half of the energy is associated with the magnetic field component.

Chapter 4 indicates that energy levels as low as 10^{-9} J (and above) appear to have small or subtle effects on weak chemical bonds, ligand receptor interfaces, cellular transport mechanisms, and so on. In a cellular volume of approximately 8×10^{-9} cm^3, an electromagnetic wave with a magnetic flux density of 1 mT, and an electric field intensity of 300 kV/m would have a total energy of 0.636×10^{-14} J (by combining 0.318×10^{-14} J from the electric field component and 0.318×10^{-14} J from the magnetic field component). Energies associated with this electromagnetic wave, and its field components, appear to be much too low to have even small or subtle direct effects on chemical bonds in biological

systems. But we know that electric, magnetic, and electromagnetic fields with these magnitudes do have significant impacts on biological systems. So, some of the mechanisms must involve movement of cellular components and molecules rather than a direct influence on bonds.

As indicated previously, electric fields at and above 100 V/m can move cell receptors from one location to another. Also, extremely small electric fields can move charged particles between atoms, cells, tissues, and organs. The movement of positively charged hydrogen ions, even with very low electric field intensities, can promote electro-osmosis and contribute to the movement of water from an injury site or a tumor [1]. Extremely small magnetic fields can influence the direction of moving charged particles. Research has shown that combinations of static and time-varying magnetic fields in the range of 13 to 114 μT can influence and interact with Ca^{++} ion channel proteins in the cell membrane [2], and 50-μT magnetic fields at 50 Hz can inhibit metabolic and mitochondrial activity [3].

Many of the observed biological effects associated with low-intensity electric, magnetic, and electromagnetic fields can be classified as subtle energy phenomena. Standard field or kinetic equations applied to subtle energy phenomena often do not predict or verify the experimental results that are observed. For instance, Adair [4] states that weak low-frequency electric and magnetic fields cannot directly produce biological consequences on cellular DNA. To prove his point, Adair assumes a small applied external field, E_a, of 1 mV/m, a cell radius, r_C, of 10 μm, a cellular cytoplasm resistivity, ρ_I, of 1 Ωm, and a conductance per unit area associated with the cell membrane, G_M, of 5 S/m. He then calculates the internal electric field for the cell, E_I. Using the relationship

$$E_I = E_a r_C \rho_I G_M \tag{5.4}$$

Adair calculates a cellular internal electric field intensity, E_I, of 7.5×10^{-8} V/m. He also calculates the electric field intensity for the cell membrane, E_M, that is induced by the applied external field, E_a, using a cell radius of 10 μm and a cell membrane thickness, d_M, of 7 nm:

$$E_M = E_a r_C / d_M \tag{5.5}$$

The calculated value for E_M is 1.4 V/m. This value is almost 18 million times larger than the cell's internal electric field intensity, E_I. In fact, if the 70-mV potential across the cell's plasma membrane is divided by a membrane thickness of 7 nm, and the electric field associated with the cell membrane is 10 MV/m. Combined with a calculated membrane resistance per unit area of approximately 0.14 to 15 Ω/m^2, these field and resistance per unit area values

supposedly shield the internal components of the cell from the effects of externally applied electric fields [5]. There is only one problem with this conclusion. As previously shown in a rather large number of references cited in these chapters, we actually do observe, detect, and measure effects associated with internal cell components when relatively low-level electric fields and low-level electric currents are applied to cells and tissue.

But going a little further with Adair's analysis, using electric field theory, if we assume a surface charge density, ρ_S, for a cubic cellular organelle with dimensions of 2 μm on each side, the total surface charge for one side of the organelle is given by the expression, $Q \approx 2$ (Area) $D_I = 2$ (Area) $\varepsilon_O \varepsilon_R E_I$. Considering a relative dielectric constant, ε_R, of 80, the surface charge, Q, for one side of the organelle is 42.4×10^{-29} C. Dividing this number by 1.6×10^{-19} C /e$^-$ charge yields 26.5×10^{-10} electron surface charges. If the RMS current, I, is obtained from instantaneous current, i,

$$i = dq/dt = d\left[Q\sin(\omega t)\right]/dt = Q\omega\cos(\omega t),\ I = \omega Q/(2)^{1/2} = (2)^{1/2}\pi f Q \tag{5.6}$$

at a frequency, f, of 50 Hz, the current would be 0.9×10^{-25} A, or approximately 18 electrons per year. Based on these calculations, Adair claims that no direct biological effects can occur with these low-level fields. But, again, this conclusion appears to ignore and deny biological effects that are actually measured and observed with the application of low-level electric fields.

Adair also uses the Faraday effect to show that magnetic flux densities in the μT range induce electric fields, E, that are much too small to have biological effects:

$$E = r_C\ \omega B/2 \tag{5.7}$$

At 60 Hz, considering magnetic flux densities of 5 μT and a cell radius, r_C, of 10 μm, Adair indicates that the resulting induced electric field of 0.01 μV/m is much too small to support the claim that magnetic fields, with magnetic flux densities in the μT range, could have biological consequences. However, again, published research indicates that magnetic fields at μT levels and lower, and electric fields less than 1 mV/m can have significant impacts on biological systems, right down to the cellular component and molecular level [2, 3, 6–8].

In some cases, Adair appears to have a point regarding "direct effects." But why do the well-known fundamental relationships of (5.4) through (5.7) fail to predict biological consequences, when we know these biological consequences do exist at the molecular and cellular level and are used in a variety of

electrotherapeutic and magnetotherapeutic applications? One answer points toward oversimplifications and inaccuracies in our models of the cell. Apparently, contrary to conventional assumptions, the cell membrane does not electrically isolate the interior of the cell from electrical activity at the exterior. For instance, cell membrane ion channels can promote significant levels of ion transport through certain regions of the cell plasma membrane. Ion channel transport mechanisms and ion channel structure can be influenced by low-level externally applied electric fields or charge accumulation. In addition, externally applied fields can promote changes with respect to receptor location and charge accumulation on cell receptors. These receptor changes can have significant effects for a variety of intracellular signal pathway mechanisms associated with metabolism, proliferation, differentiation, and apoptosis where the mechanism is influenced by processes associated with certain cell signaling pathways.

Engström and Fitzsimmons describe a number of experiments that can provide insight into transduction processes where magnetic or electric fields are converted into biological signals [9]. They show support for the effects of low-level electric fields (less than 0.2 mV/m) on calcium signaling in lymphocytes, and low-level magnetic fields (less than 2 μT) on the antiproliferative effects of a chemotherapeutic agent (Tamoxifen) in a breast cancer cell line (MCF-7).

Experimental evidence discussed in previous chapters has shown that the application of very low-level dc electric fields and currents can influence the production of ATP and various enzymes, cell apoptosis, and cell proliferation. Obviously, the low-level electric fields are influencing structures and organelles located in the interior of the cell as well as structures located on the cell membrane surface. Based on experimental evidence and what is known about cell membrane structure, the assumption that the interior components located in the cellular cytoplasm are electrically isolated from exterior applied fields appears to be faulty. In addition, many of the assumptions concerning the cell interior are made based on the cytoplasm having the characteristics of a saline solution, very similar to ocean water. The old saying, "We carry the sea with us," has been used for years to describe the interior of cellular cytoplasm. That cute little saying (very popular with evolutionists) may be somewhat inaccurate if the cell cytoplasm is more like a gel that undergoes phase changes.

5.3 The Derivation of Design Equations That Could Be Useful in Magnetotherapy: From Subtle Energy Levels to Not-So-Subtle Energy Levels

Can we come up with models and derive relationships that will help to predict biological impacts of low-level electric and magnetic fields? Yes we can. In

Chapter 4, (4.9) and (4.10) show relationships between combinations of very low-level pT magnetic fields, induced currents, and associated frequencies that appear to have therapeutic value in treating Parkinson's disease and non-trauma-induced epilepsy.

Let us start out in a more rigorous fashion than we did in Chapter 4 and derive (4.10) for an individual electron charge in a collection of coordinated moving charges that are all influenced and maintained in a coherent fashion by the same magnetic field. The basic model for the applied magnetic field and associated electron motion is shown in Figure 5.1. Notice, the waveform is set

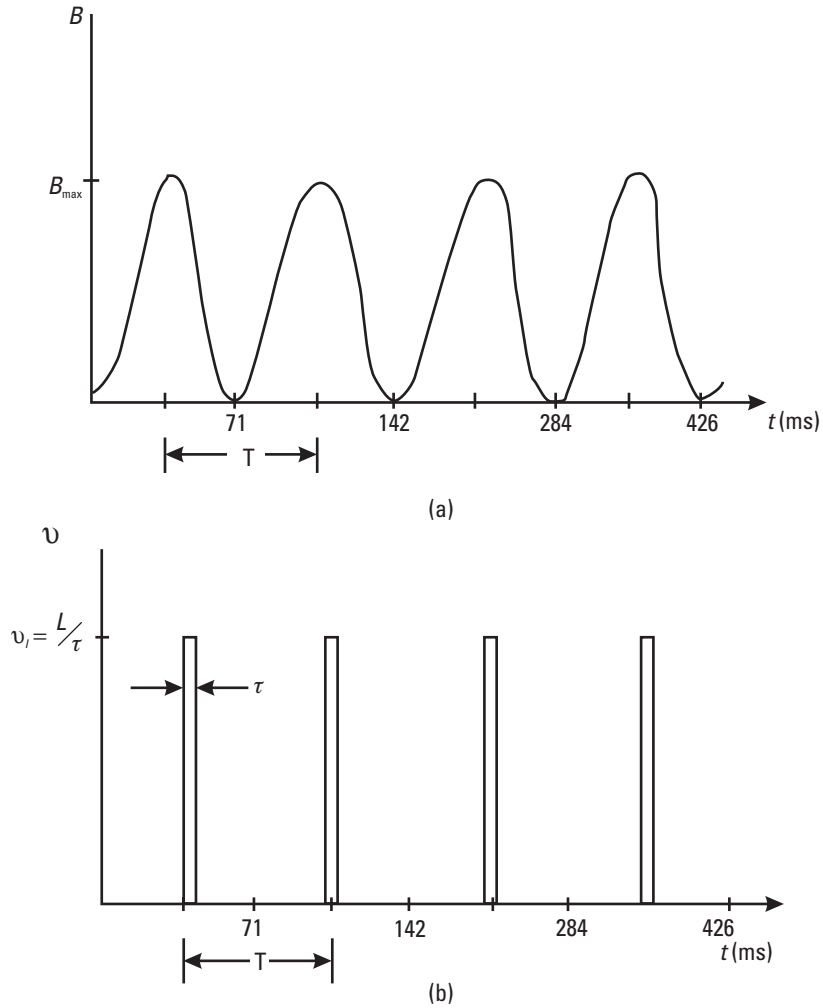

Figure 5.1 (a) Applied magnetic field sinusoidal signal. (b) Resulting discrete electron velocity model for an electron that is hopping from site to site in a nerve fiber protein.

up so that the force on the electron is in the same direction when the magnetic field is close to its peak value. The electron moves a very short distance, L, during a very small part, τ, of the total time associated with one period of the waveform, T. We will assume that the electron is very weakly bound to each site and that its site-to-site hopping velocity is reasonably close in value to the electron's thermal velocity. Under the influence of the applied magnetic field, each charge hops from site to site over distances of 10Å, L, during time increments, τ, of 0.42×10^{-14} seconds.

Using the relationship between an unbounded Lorentz force, $-q(E + v \cdot B)$, and the external force on a charged particle that has wave-like properties in a conducting medium, $(h/2\pi)(dk/dt)$, we can derive a subtle energy relationship. In this relationship, h is Planck's constant, k is $2\pi/\lambda$ (where λ represents wave length), B is magnetic flux density, and v is velocity. We will assume that the phase velocity, v_P, group velocity, v_G, and instantaneous velocity, v_I, are the same for the very short distances, L, involved and $v_P \approx 2\pi\nu/k$, where ν is a frequency term. Assuming that the contribution from the electric field component is negligible, and ignoring the negative sign and force vector,

$$\text{Momentum for charge (electron) with wave-like properties} = P = (h/2\pi)k \text{ (De-Broglie relationship)} \tag{5.8}$$

$$F_C = \text{External force on a charge (electron) with wave-like properties} = dP/dt = (h/2\pi)(dk/dt) \tag{5.9}$$

$$F_U = \text{Unbounded Lorentz force from applied magnetic field} = (q)(v_I B) \tag{5.10}$$

There is a temptation to make F_C equal to F_U. For this application, that would not be appropriate for a continuous dk/dt term as it relates to the unbounded Lorentz force. However, let us do it anyway. Let us make them equal and see where that assumption runs into trouble.

$$\begin{gathered}\text{Force of electron with wave-like properties} = (h/2\pi)(dk/dt) = (q)(v_I B) \\ \text{Momentum for electon with wave-like properties} = (h/2\pi)dk = (qBv_I)dt\end{gathered} \tag{5.11}$$

$$hdk = (2\pi)(qB\, dL/dt)dt \tag{5.12}$$

where $v_I \approx dL/dt \approx L/\tau$, L represents the electron site-to-site hopping distance, and τ represents the site-to-site hopping time.

$$\hbar dk = (2\pi)(qB)dL \tag{5.13}$$

Now, let us integrate both sides. But, wait! We need to recognize one little peculiarity of this model. Notice that the right-hand sides of (5.12) and (5.13) are discrete. Over one time period, T, the term on the right-hand side only involves a small distance, dL, for a very short period of time, τ, as indicated by Figure 5.1(b). Consequently, it is active only during a very small time duration associated with the continuous excitation function (applied magnetic field) that is shown in Figure 5.1(a). In other words, the right-hand side involves a very small time increment over the total period of the applied magnetic field signal. But, the left-hand wave function side is continuous. Both sides need to reflect the discrete aspect. To do this, a (τ/T) averaging term needs to be applied to the continuous left-hand term in order to make it compatible with the discrete right-hand term. Also, as we go further, the integration operation eventually results in an energy equation and the (τ/T) ratio appropriately relates the left-hand side of the equation to average energy ($W_{AV\ WAVE\text{-}LIKE}$). Therefore, integrating both sides of (5.13), we have

$$\begin{aligned}(\tau/T)\int \hbar dk &= \int (2\pi)(qB)dL \\ (\tau/T)\hbar k &= (2\pi)qBL\end{aligned} \tag{5.14}$$

Since $k = 2\pi/\lambda$, $\lambda = v_P/\nu$ (where ν is the frequency associated with the thermally excited electrons, which is approximately 0.64×10^{13} Hz) and $v_P \approx v_I$,

$$\begin{aligned}(\tau/T)\hbar((2\pi)/\lambda) &= (2\pi)qBL \\ (\tau/T)\hbar(\nu/v_P) &= qBL \\ (\tau/T)\hbar(\nu/v_I) &= qBL \\ W_{AV\ WAVE\text{-}LIKE} &= \hbar(1/T)(\tau)(\nu) = qBv_I L\end{aligned} \tag{5.15}$$

And since the frequency, f, for the applied magnetic field waveform is equal to $1/T$,

$$W_{AV\ WAVE\text{-}LIKE} = (\hbar)(f)(\tau)(\nu) = qBv_I L \tag{5.16}$$

The left-hand side of (5.16) looks vaguely similar to the Einstein equation (Energy = hf or $h\nu$), but it has some strange-looking extra terms. However, with the thermal excitation frequency, ν, value of 0.64×10^{13} Hz, a site-to-site hopping time, τ, of 0.42×10^{-14} sec, magnetic flux density of 7 pT, a frequency of 14 Hz, v_I of 2.38×10^5 m/sec (obtained by dividing L by τ), and a site-to-site hopping distance of 10Å, we find that the left-hand side and right-hand side of (5.16) are approximately equal. Therefore, for the parameter values assumed, if we consider the $(\tau)(\nu)$ product to be constant over the range of pT magnetic flux densities of interest, (5.16) can be simplified to

$$W_{AV\ WAVE\text{-}LIKE} \approx (1/11\pi)hf \approx qBv_I L \tag{5.17}$$

At this point you might say, "cute little fudge factor you have there, O'Clock!" Well, yes; but it appears that no serious violations of physics or mathematics have been introduced in the effort to derive this expression. Along with other equations, (5.16) and (5.17) can be used to make estimates for a limited range of frequencies and pT magnetic flux densities. I am not looking for total agreement, approval, or applause here; I am just trying to develop a few design tools for subtle energy devices and therapeutic protocols.

At this point we have a mix of quantum concepts and electromagnetic field theory, providing an energy relationship that could be useful in the design process for estimations. Once calibrated, the relationship can help to relate the frequency with an appropriate magnetic flux density for subtle energy pT magnetotherapy applications.

Now, we have a family of equations that can be very helpful in the initial design process for magnetotherapeutic devices and protocols that "should not work" according to some experts. But these therapeutic devices and protocols do work, and they are fairly consistent. So, as engineers, we are charged with the duty to develop an engineering design pathway for these devices and protocols, and eventually provide the therapeutic benefits that they offer.

From Chapter 4, (4.6) and Faraday's law will give us reasonable estimates of the electric fields that we can anticipate from the application of pT magnetic fields. Equations (4.7) and (4.9) will give us estimates for the current density and current levels that we can anticipate from pT magnetic fields and any induced electric fields. Equation (4.8) would be useful as a first estimate for coil design, coil distance from cranium, and so on. And (5.17), in this chapter, provides additional information required for the design process. It gives a good estimate for the specific magnetotherapeutic frequencies that could be associated with various applied pT magnetic fields. The calculated induced current and current density levels appear to be compatible with published research concerning synaptic junction response times, density of charged molecules at synapses,

current density, and current levels associated with synapses and various neuron components in the brain. This simple model can give us a clue concerning what components and regions of the brain can be affected by the applied pT magnetic fields.

Let us now make a jump of a factor of 1 million, to the μT level. MicroTesla (μT) magnetic flux densities are still in the subtle energy category. If we calculate the energy for a 1-μT magnetic flux density in a cell volume of 8×10^{-9} cm^3, according to (5.2), we would be dealing with energies of 0.318×10^{-20} J. Although this energy level cannot have direct effects on weak chemical bonds, μT magnetic fields appear to have an influence on ion transport mechanisms through ICR or IPR mechanisms. As is shown in (4.5), the relationship between the applied frequency, or resonant frequency, f_{ICR}, the magnetic flux density, B_Z, and the charge to mass ratio, q/M, for the ion that is being influenced by B_Z, is as follows,

$$(f_{ICR}) = (q/2\pi M)(B_Z) \tag{5.18}$$

Deriving the radius and circumference for the ion pathway under the influence of ICR or IPR yields dimensions that are in meters. This indicates that at the cellular level, the pathway for an ion that is being transported through a cell membrane ion channel, under the influence of ICR or IPR, is essentially a straight line. That is just what we want for ion transport mechanisms involving narrow ion channels. ICR and IPR models would tend to confine μT magnetic field activity to relatively short pathways for ion transport across very thin tissues and cell membranes.

Let us go up another factor of 1,000 to the mT level. Now, the energies are not so subtle, and both the magnetic field and induced electric field are quite significant. Within the confines of a cell volume, magnetic flux densities of this magnitude are associated with energies that are above thermal noise levels. Magnetic field flux densities above 20 mT can produce energies strong enough to influence weak chemical bonds. Electrical currents produced by the induced electric field component, associated with mT magnetic flux densities, can have significant impacts on intercellular communication, cell proliferation, immune cell activity, cancer promotion, tumor growth inhibition, and apoptosis [10–14].

Finally, when we reach the 1T range and above, for therapeutic applications, we are at the level utilized by repetitive transcranial magnetic stimulation (rTMS), which has been useful in the treatment of depression. In this case, the electrical effects induced by magnetic fields at the 1T level are so pronounced that they can depolarize nerve cells in nerve fiber and affect action potentials.

5.4 The Impact of Integration and Summation Processes: Is the Noise Level Really a Lower Limit?

The answer to the above question is "no." Any time I read a paper that states a specific level or process cannot have biological impacts because the signal level is below the noise limit, I generally throw the paper away. Using signal-to-noise enhancement techniques, communication, radar, and sonar systems have been detecting and processing signals with amplitudes that are below the noise limit (sometimes by a factor of 1,000 or more) for more than 50 years. Biological systems have been utilizing a variety of signal-to-noise enhancement techniques for eons.

One of the basic processes that helps to overcome the so-called noise limit and promotes signal-to-noise enhancement involves summation or integration of coherent and noncoherent signals. In communications, radar, and sonar, the integration or summation process variable is usually time. In imaging applications, the integration or summation process variables can involve space, or both space and time. Summation and integration can be found in the senses and also as a part of neurological processes that occur in many other biological functions. The soma of a neuron is often mathematically modeled as a summation or integration device.

Let us use a simple example of a signal-to-noise enhancement using the process of discrete summation. This is similar to the kind of enhancement that is achieved with the use of transversal filters or matched filters in spread spectrum communication system and pulse compression radar applications [15–17].

Figure 5.2(a) shows the basic components of a neuron [18, 19]. For the engineering model of the neuron [Figure 5.2(b)], we will assume that multiple dendrites feed into the soma, and each dendrite input to the soma has a weighting function. The weighted inputs are summed (Σ), and the sum signal (y) serves as the input signal to the processing and transfer functions [Figure 5.2(b)]. The processing function could be something as simple as a hard limiter decision element, or it could be more complex. What is unique about this system is that it can operate in the same manner as a transversal filter or matched filter [Figure 5.2(c)]. It can add the signal components (we can use 1V signals for ease of computation) in a coherent manner (y_{SIGNAL} = 1V + 1V + 1V + 1V + 1V + 1V + 1V + 1V + 1V = 9V). And at the same time, this device can add the noise level components (we will assume a 1 V_{RMS} noise level) that occur with each signal pulse in a noncoherent manner ($y_{NOISE} = [(1V)^2 + (1V)^2 + (1V)^2 + (1V)^2 + (1V)^2 + (1V)^2 + (1V)^2 + (1V)^2 + (1V)^2]^{1/2} = 3V$). Notice that the signal adds up in a more efficient manner (coherent addition) than the noise (noncoherent addition). Signals add coherently (i.e., 1V + 1V = 2V). Noise adds noncoherently (i.e., $[(1V)^2 + (1V)^2]^{1/2} = 1.414V$). Thus, by employing a transversal filter summation or

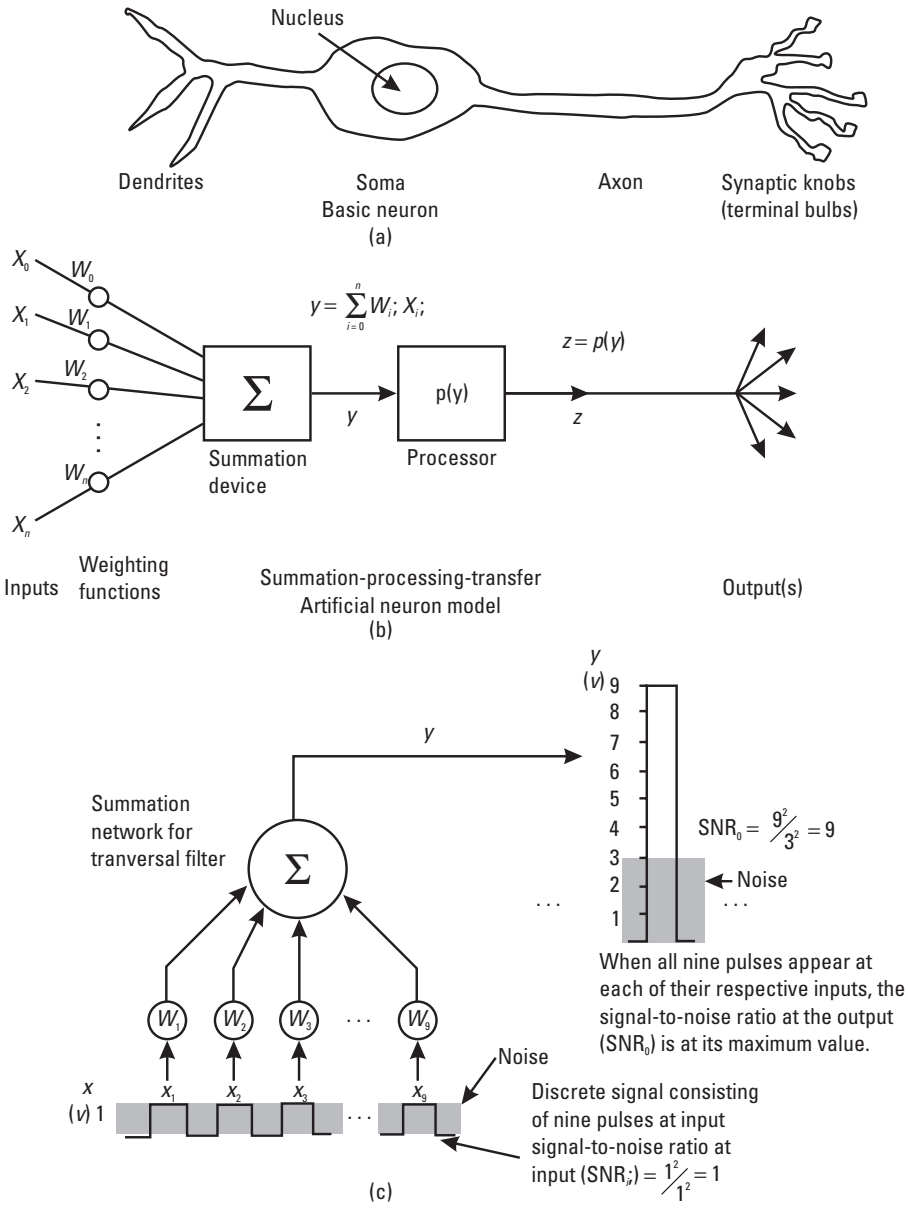

Figure 5.2 (a) A typical neuron (nerve cell) showing the basic components. (b) The engineering model block diagram for a neuron (or artificial neuron). This simple neuron model shows the signal inputs and weighting functions (representing the dendrites), the summation network (input side of the soma), and a processing and transfer function (output side of soma and axon). (c) Transversal filter representation of the simple additive or integrative portion of the neuron model.

integration device, the signal-to-noise ratio at the output of the filter can be significantly improved over the signal-to-noise ratio at the input of the filter. In this case, the signal-to-noise improvement is a factor of $9[(9V/3V)^2/1^2]$, with the coherent addition of nine properly sequenced pulses. For biological systems, Adair mentions the advantages of integration and summation, in an electric field environment, on signal-to-noise ratio. He states that if a field acts on N ions for a short time, the ratio of the mean distance the ion is moved by the field to the mean random translation, the signal-to-noise ratio will be a function of the square root of N. For sufficiently large numbers of ions, the signal will be observable [20].

Another method that can promote biological system responses to very weak signals is stochastic resonance [21, 22]. In some stochastic resonance situations, random noise can assist in improving the signal-to-noise ratio for certain systems and specific nonlinearities [22]. In others, random noise can boost a weak force or a weak signal just high enough to produce an observable, detectable, or useful event. To illustrate stochastic resonance, imagine a charged particle, confined to a specific molecular site, moving back and forth between the energy boundaries of a molecule (Figure 5.3). The back and forth motion is caused by a weak sinusoidal signal or weak sinusoidal force. In this bistable system, the charged particle does not have quite enough energy to surmount the barrier to go to the next site. However, a random noise signal is coupled to the charged particle and if the particle's small amount of rocking motion helps it to arrive at just at the right spot in the potential well, the very small amount of additional energy from the noise signal could push it over the top of the molecular site 1 energy well and into the next molecular site, the site 2 energy well. The site-to-site movement would be random within the period of the sinusoid, but there would most likely be a movement to the next site within the time frame of one period. This model is somewhat like the model used for (5.17) except the roles of the coherent weak excitation signal (pT magnetic flux density) and random vibrations are reversed.

5.5 Summary

When dealing with subtle energy phenomena, conclusions concerning biological relevance, which are based on conventional energy relationships and models, are often either incomplete or inappropriately applied. Integration, summation, and stochastic resonance processes must be considered before conclusions based on biological impact or signal-to-noise limitations are made. Additional accuracy problems are encountered in subtle energy relationships due to oversimplifications and inaccuracies in conventional cell models.

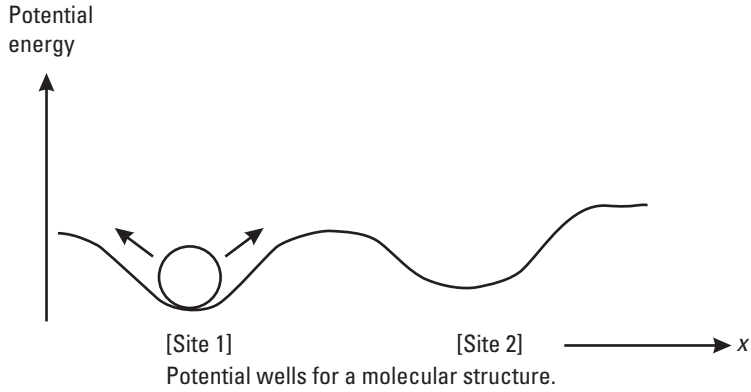

Figure 5.3 Charged particle in a bistable system that is only able to move back and forth in a confined energy well under the influence of a weak signal.

Exercises

1. Equations (5.16) and (5.17) don't seem to agree with kinetic energy relationships. From the equation $W_{AV\ PARTICLE} = (\tau/T)(1/2)mv_I^2$, where m is the rest mass of the electron, the average energy is about 5.6 times greater than the average energy calculated for the electron with wave-like properties. Why is there a difference?

   The comments that I have received from several biophysicists concerning (5.16) and (5.17) are interesting. One of them said, "George, those equations look a little wild, weird, and flaky." My reply was, "Wild, weird, and flaky! The foundations for those two equations can be found in sophomore physics books and junior solid-state physics books. And those equations require no wild assumptions. I'll tell you what is wild and weird. I have recently heard you and your colleagues discussing string theory, the space-time fluid, the Higgs field, loop quantum gravity, instantaneous appearance and disappearance of matter in quantum theory, dark matter, dark energy, multi-universes, singularities, tachyons, and a host of ideas that go way beyond wild and weird. Now, let's discuss some items that are really flaky. Let's talk about the use and abuse of statistical tools in clinical trials, and the credibility and ethics of the double-blind clinical study technique." (We will go into more detail on this in Chapter 8.)
2. For this example, use the mks system. Some time ago, I was told that an equivalent resonance mechanism occurs at the pT level. The idea goes something like this: W (Energy) $= mc^2 = mv_P^2 \approx qBv_GL$ (where the phase velocity, v_P, is approximately equal to the group velocity,

v_G). Therefore, since $v_P \approx v_G$, $mv_P \approx qBL$. Assuming that the resonant frequency, f_R, is a function of radius, r, in a cyclotron resonance type of mechanism, $f_R = v/2\pi r$; $m(2\pi r f_R) \approx qBL$. Now, $f_R = (v/2\pi r) \approx qBL/m(2\pi r)$. In this case, we allow r to equal L. The equation for the applied frequency associated with a pT magnetic field is now given in a resonance relationship, $f_R \approx (q/2\pi m)B$. For a limited range of frequencies and pT magnetic flux densities, the relationship between f_R and B appear to work even better than what (5.16) and (5.17) predict. But, going back to the beginning and looking over the first three equalities and the assumptions regarding velocity, do you see any flaws in the initial assumptions with this derivation? Keep in mind, just because the numbers work out, that does not always mean that the relationship applies, or is even correct.

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6

Primary Design Drivers for Electrotherapeutic Devices

6.1 Electrotherapeutic Device Design Concept

The steps in an engineering design process [1–3] often involve the following (not necessarily always in this order):

1. *Recognizing a need:* If something is unsatisfactory, unsafe, uneconomical, unpleasant, unhealthy, too slow, smells bad, tastes bad, and so on, then how can the situation, condition, or device be improved or corrected?
2. *Defining the problem:* Goals and objectives are defined and established; economic, manufacturing, and user physical constraints are determined, as are safety issues.
3. *Gathering the information:* This includes historical issues, legal issues, other design approaches, codes and standards, research results, mathematical models, inputs from sales, marketing, and manufacturing, costs, and impact on addressable and available market.
4. *Conceptualizing alternative approaches:* Design options are evaluated that are within present capabilities, "form and function" models are developed, time limits are specified, interaction with manufacturing is initiated, design and performance specifications are outlined, and initial patent issues are addressed.

The first three design process steps, along with part of the fourth, are often considered to be some of the primary components of the design concept phase.

Once the design concept phase has been completed, the remainder of the tasks in step 4 are completed followed by the remaining steps in the design process:

5. *Evaluating the alternatives:* Analytical tools, cost estimates, time-to-completion estimates, reliability considerations and analysis, evaluation of quality control issues, and distribution plans are initiated.
6. *Planning the project:* This is ongoing once the problem definition process has been initiated; and task identification, order of priority, choice of scheduling tools, timelines, allocation of responsibilities, allocation of planned expenditures, contingency plans, assembly and testing protocols are initiated.
7. *Selecting the preferred alternative:* Incorporating user values, preferences, and priorities, final decisions made based on prototype studies, design concept verification phase, patent documentation submitted, advertising plan initiated, distribution plans finalized, design and performance specifications finalized.
8. *Communicating the design:* This is ongoing and requires the establishment of a network of interconnected communication channels with manufacturing, sales, marketing, regulatory agencies, and the user/customer, advertising plan is finalized;
9. *Implementing the preferred design:* Design and performance specifications finalized, assembly and testing protocols finalized, and manufacturing resources in place.

In design classes associated with engineering, interior design, and art, the "design concept" tasks are often used and defined incorrectly. A design concept does not initially concentrate on the thing or item being designed. A design concept involves a large part of the beginning of the design process, and it often requires much more thought and structure concerning the following:

1. What are the operating environments for the item to be designed?
2. Who or what is going to operate and sustain the item?
3. What are the tasks that the item is supposed to perform?
4. How is the item supposed to interact with or complement other facets of the operating system?
5. What are the cost and manufacturing limitations?

6. What are the legal and patent issues?
7. What are the addressable and available markets?
8. What kind of time limits need to be addressed?

The design concept incorporates the design drivers, often considering the functions and constraints that ultimately determine structure. The design concept must focus on limits, constraints, and point of view. For instance, Michelangelo purposely introduced some disproportion in his statue of David because he realized people would be looking up at this relatively tall statue. If the artistic task is to paint a battle scene, the size of the canvas and the color scheme should be considered before the painting begins. A small canvas will probably not be sufficient for a large battle scene. And large amounts of yellow and pink would probably not be the primary color combination that an artist would want to use for this kind of painting.

The operating environment is important to consider in the initial design concept phase. For instance, assume the design task involves designing a chair, and the designer initiates the effort by planning an elegant Chippendale with graceful curved legs and a large amount of intricate rococo ornamentation. Sometime later, the designer finds out that the chair must support a weight of 350 pounds, and it must withstand the punishment of a smack-down wrestling event. It is obvious that the design concept component involving the operating environment and the task at hand were not given enough consideration before the Chippendale design decision was made.

6.2 Electrotherapeutic Device Output: Constant Current, Voltage Range, Frequency Choices, and Waveform Design Considerations

One of the strategically important device features for many electrotherapeutic applications involves the electrotherapeutic device's ability to function as a nonideal constant current source. In this case, the peak amplitude of the output current remains reasonably constant over a relatively wide range of impedance values. In many applications (for instance, certain visual diseases), the electrotherapeutic device must be capable of delivering a relatively constant current over a wide range of combined contact and patient load impedances. Otherwise, significant patient discomfort can occur as current increases due to improvements in contact quality and reductions in tissue impedance. Under these conditions, upper limits for applied current levels could be exceeded.

Some of the higher current applications, served by transcutaneous electrical nerve stimulation (TENS) devices, utilize 10- to 35- mA current pulses. Over a period of time (30 minutes to 2 hours), these current levels (with

associated current densities greater than 0.5 mA/cm^2) can produce skin burns under gel-type surface electrodes [4]. The results reported by Patriciu et al. [4] indicate that the skin burns appear to have an electrochemical origin.

Laboratory tests have revealed that some microcurrent electrotherapeutic devices are not constant current sources at all (as shown in Figure 6.1). As previously indicated, this lack of current control can produce serious patient safety concerns, especially if these devices are being applied toward the treatment of visual system health problems.

As tissue is treated with an electrotherapeutic device, the variability associated with combinations of healing processes, movement of water, tissue structural changes, polarization variations, and contact quality can produce significant impedance changes during a relatively short 10-minute electrotherapy treatment time. Structural changes associated with electrically stimulated tissue have been shown in Chapter 2 (Figure 2.5). In addition, at

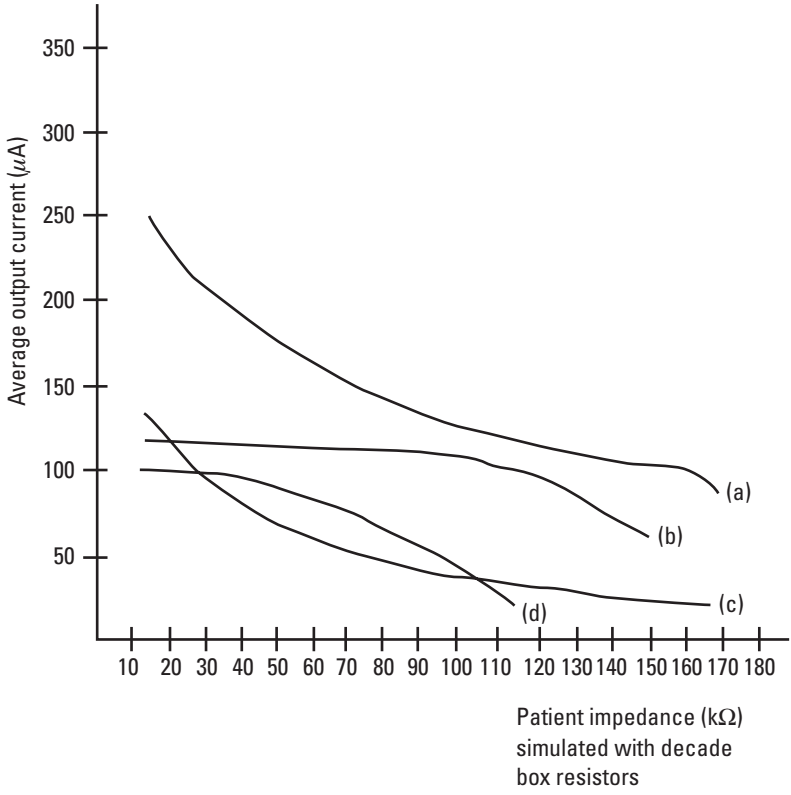


Figure 6.1 Average output current versus tissue load impedance characteristic for a number of electrotherapeutic devices. Only one of the device output characteristics (b) could be considered as a constant current source characteristic for a reasonable range of tissue impedances.

microcurrent levels, a total patient load impedance decrease from 100 to 40 kΩ (or less) is often observed at very low frequencies. As indicated previously, tissue healing, release and movement of water, the transport of ions, and improved contact quality can contribute to the observed patient load impedance decrease during an electrotherapy session involving microcurrent levels.

The range of device output voltages will be determined by the specifications imposed on the upper value of current (driven by safety considerations), the lower value of current (driven by lower limit of therapeutic efficacy), and the range of anticipated device-load impedance values (dependent upon patient tissue condition and electrode contact quality). For instance, we might consider an electrotherapeutic device peak output current magnitude specification of 100 μA, with an allowable magnitude variation of ±50 μA. This is a reasonable level of current control (±50%) over a relatively wide range of patient tissue impedances. If approximately 90% of patient impedance levels are expected to fall within the range of 15 to 90 kΩ, a battery power supply voltage of 9V and a device output series resistance (current limiting resistance) of 60 kΩ would provide a lower peak current of 60 μA and an upper current level of 120 μA. These current levels would be well within the ±50% specified operating range for peak device output current. Since many electrotherapeutic applications require a bipolar pulse, a battery power supply of slightly more than ±9V would be required. If a lower voltage battery power supply is desired, a 6V output voltage combined with a current limiting device output series resistance of 25 kΩ would supply a lower peak current of 52 μA and an upper current level of 150 μA. A bipolar output waveform would require a battery power supply of slightly more than ±6V. Notice, as the values for the supply voltage and series resistance decrease, the output current variation tends to increase and approach the ±50% variation limit when a simple series resistance is used as a combined current control and current limiting device.

From a safety standpoint, if very low patient tissue impedances are encountered, calculated values of worst-case current levels can exceed designated safety margins.

Battery power supplies are required for most electrotherapeutic applications. A plug-in unit could encounter significant problems with too much noise interference and 60-Hz leakage for some applications. A plug-in feature is generally used for battery charging while the electrotherapeutic device is not operating.

The design choices for frequency and waveform have been empirically determined. There have been some efforts to model and analyze waveform shapes and frequencies in order to find an optimum therapeutic combination. However, much of this information has been determined experimentally. For instance, a significant amount of literature dealing with clinical applications of

electrical stimulation for the past 2,000 years indicates that dc is very effective in addressing a variety of health problems. The dc sources of electric current have ranged from electric eels and Leyden jar charge storage devices (short duration) to electrochemical batteries (long duration). Direct currents of 200 μA to 1 mA have been used to treat chronic leg ulcers and ischemic skin ulcers [5, 6]. Direct current levels below 70 μA and above 200 μA have been used to treat diseases of the visual system [7–9]. Direct currents in the range of 10 μA to 120 mA have been used to treat malignant and nonmalignant tumors [10–12]. From the experience of many health care practitioners over the past 2,000 years, it appears that a dc component is very desirable for many electrotherapeutic waveforms. One of the reasons why dc or very low frequency waveforms may be so important in many applications is that they may be more compatible with the relatively slow transport of ions and any associated electro-osmotic flow of water over relatively long distances. On the other hand, ac electro-osmotic flow (at higher frequencies) might tend to support the movement or secretion of water over relatively short distances.

The best waveform shape and frequency for specific applications in electrotherapy have been discussed and debated for more than 80 years. Biedebach and Omura propose that rapid initial voltage and current rise times associated with monophasic and biphasic (monopolar and bipolar) electrotherapeutic waveforms should be more effective in opening voltage sensitive ion channels and promoting rapid charging of the cell membrane capacitance [13, 14]. In addition, they discuss the effects of pulse durations of 60 μs to 1 ms (to promote a maximum charge on the cell membrane capacitance) using pulse repetition rates of 1 to 3 pulses per second, with treatment times ranging from 15 minutes to 1 hour.

For example, we might consider the Electro-Acuscope, which appears to be a good representative for a more sophisticated electrotherapeutic system or device design. My own experiences and the experiences of family members with the Electro-Acuscope system have been very positive. For the electrotherapeutic treatment of adhesive capsulitis, plantar fasciitis, sciatica, knee injuries, colitis, and various infection problems, it is difficult to find another electrotherapeutic device that matches the therapeutic efficacy provided by the Electro-Acuscope. According to Braun [15], the Electro-Acuscope uses a very short duration spike (overshoot) at the leading edge of each current pulse (approximately 100 to 300 μsec in width) to open the fast response ion channels. A relatively long duration current pulse plateau of approximately 2 to 200 ms is also utilized to optimize the opening of the slower ion channels. In some operating modes, information in the Electro-Acuscope technical manual indicates that biphasic fast pulses, in the 1- to 3-MHz frequency range are also superimposed on the rectangular pulse output waveform to penetrate the stratum corneum layer and to open specific cell membrane ion channels.

Some research suggests that fast rise-time short-duration electrical pulses are more effective in opening voltage sensitive calcium channels in sensory neuron cell membranes [16], while longer duration pulsed waveforms are more effective for voltage-sensitive calcium channels associated with fibroblasts [17]. The voltage-sensitive ion channels appear to help initiate or accelerate biochemical processes involved in cellular repair [13]. In some applications (for certain wound healing applications and cancer treatment) a monophasic, or monopolar, waveform is utilized. In other applications (such as treatment of certain types of visual disease and neurostimulation) a biphasic, or bipolar, waveform is used. The bipolar waveform is often recommended in order to avoid polarizing effects.

The choice of dc and/or ac waveforms, along with the appropriate frequency range, often depends upon the health problem or application, electrode placement constraints and the biological transport mechanisms that are to be addressed. Direct current electrotherapy has been very effective in cancer treatment, wound healing, and visual disease applications where the transport of ions, movement of water, improvement of capillary porosity, control of pH, generation of ATP, uptake of amino acids, protein synthesis, and wound epithelialization are critically important. Direct current and very low frequency ac electrotherapy have been useful in promoting lymphatic drainage and treating edema. Frequencies in the 0.5- to 1.5-Hz range have been very effective in cranial electrotherapy stimulation (CES) and pain management [18]. Electric fields and electric currents with frequencies close to 10 Hz appear to have an effect on DNA replication, cell proliferation, lymphatic drainage, edema, reduced blood pressure, detoxification, and wound healing [19–21]. Frequencies in the range of 80 to 100 Hz have been useful in treating inflammation [18]. Electric currents and electric fields using short-duration pulses and a variety of frequencies below 110 Hz (including 72 and 105 Hz) appear to promote capillary healing, DNA synthesis, protein synthesis, and production of fibroblasts [22].

Many electrotherapeutic applications show excellent results with a simple dc output. Other electrotherapeutic applications appear to prefer a pulsed or rectangular waveform (ac) with a duty cycle of 50% or less, frequencies in the range of 0 Hz (dc) to 110 Hz, and in some cases, the incorporation of leading and trailing edge current spikes. Often, for electrotherapeutic devices that use an ac output waveform, the addition of a dc component can enhance therapeutic efficacy and/or provide other therapeutic benefits. Some electrotherapeutic devices utilize a number of waveforms and frequencies, combining them into one large complex output involving many frequencies and multiple amplitudes. Some health care practitioners are of the opinion that this approach may confuse the healing process. They feel it might not be as reliable, or as effective, as design approaches that focus on one primary waveform, one type of waveform

modulation and a narrow range of frequencies applied over a specific treatment time frame.

6.3 The "Window Effect"

Electrotherapy and magnetotherapy often exhibit the kind of "window effects" that can occur in chemotherapy, radiation therapy, and enzyme kinetics. For instance, in some cases, very low doses of chemotherapeutic agents or radiation may not be very effective in treating a malignant condition. However, a slight increase in level or dose can promote noticeable improvements in therapeutic efficacy. Then, as the dose or level is increased further, the toxicity of the chemotherapeutic agent or peripheral damage from the increased level of radiation becomes so severe, that the treatment is no longer therapeutic. But there is a "window" of therapeutic efficacy where the chemotherapy dose, or radiation level, provide the best therapeutic benefits with the least toxicity or peripheral damage. Window effects are observed in biomedical phenomena and therapeutic applications involving electric current intensity, electric field intensity, magnetic field intensity, and frequency.

Laboratory data associated with biological effects of electric, magnetic, and electromagnetic fields have shown intensity windows where biological responses occur within a certain range of intensities, while no significant responses are observed above or below the intensity range [23]. Needless to say, this kind of data is often difficult to reproduce. However, windows of enhanced protein kinase C cytosol activity have been observed in HL 60 cells at 60-Hz electric field strengths of 8 to 100 mV/cm [24]. A frequency window (30 to 60 Hz) appears to be associated with c-myc and histone H2B RNA transcripts in HL 60 cells [25]. Human fibroblast cells have exhibited proliferation enhancement, within a 10-Hz electric field intensity window of 30 to 60 mV/m, and a current density window of 3 to 8 μA/cm^2 [21]. Amplitude and frequency windows for low-level and low-frequency (10 to 150 Hz) electromagnetic fields appear to exist for mRNA transcription [26]. Lyte, Gannon, and O'Clock [27] and O'Clock and Leonard [28] reported 15-μA windows of dc intensity where malignant cell proliferation was suppressed by more than 98% over cell proliferation levels occurring on either side of the current intensity window. An example of a window effect involving the suppression of malignant cell proliferation is shown in Figure 6.2.

The interaction of two or more cell membrane receptors with electric fields, magnetic fields, electromagnetic fields, specific current densities, and accumulated charge could produce window effects. Liboff developed an ion cyclotron resonance model (see Chapter 4) that helps to explain frequency windows involving the interaction of μT magnetic flux densities with biological

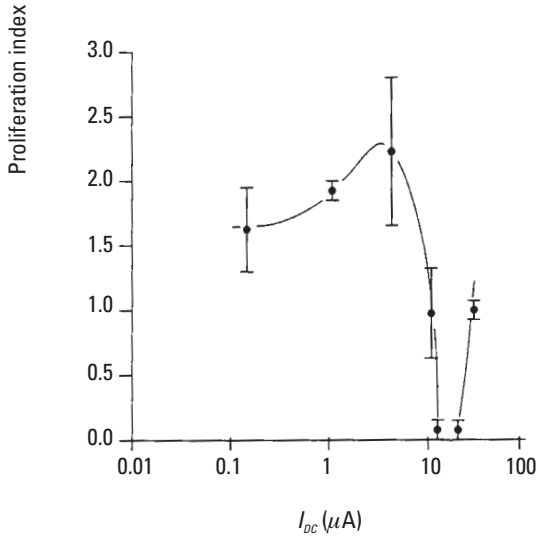


Figure 6.2 Plot of in vitro EL4 lymphoma cell proliferation (compared with a control) for direct current stimulation over the range of 0.1 to 250 μA. A significant malignant cell proliferation suppression appears to occur within a "window" of current extending from 15 to 25 μA. (*From:* [27]. Courtesy of the *Journal of the National Cancer Institute*.)

systems. A model for frequency and amplitude windows associated with magnetic fields has been developed by Zhadin and Barnes. They propose that ions in macromolecules, under the influence of dc and ac magnetic fields, promote macromolecular conformational changes when combined with changes in ion thermal motion in the macromolecule interior [29].

The consideration of window phenomena is strategically important to ensure therapeutic efficacy in electrotherapy and magnetotherapy applications. Window phenomena must be considered in electrotherapeutic and magnetotherapeutic device design, especially when issues of safety, consistency, reliability and optimization of therapeutic efficacy are considered.

6.4 Electrotherapy Device Design Process: Some Considerations and Constraints

The "weak links" associated with electrotherapeutic devices and systems often involve: (1) the probe-tissue interface (often, the probe-tissue impedance is high and variable, somewhat capacitive and nonlinear); (2) device reliability (solder joint and interconnect failures, missing or distorted waveform components); (3)

device control and decision making problems and inconsistencies (due to software-firmware-microprocessor responses to weak batteries, current/voltage deviations, and current/voltage fluctuations due to different patient impedance characteristics); (4) output monitoring capabilities (showing voltage and current levels, waveform); (5) deficiencies in human engineering (including too many control buttons and switches, small letters and numbers on displays and switch/knob controls, probe/connector insertion difficulties, inadequate or very poorly written instruction manuals); and (6) customer service and follow-up for operating problems and intermittent failures.

All too often, when electrotherapeutic device cost estimates and pricing policies are being considered, costs associated with documentation, manuals, customer education, service/follow-up, publication, and periodic certification are not considered or factored into the pricing plan. Failure to consider these costs can prevent a company or product from ever becoming profitable. Documentation, such as test procedures, operating manuals and manufacturing procedures must be considered as part of the continuing design and development process. Poor documentation impedes the implementation stage that follows device and protocol design.

6.4.1 Some of the Design Concept Issues to Be Considered

When addressing design concept issues, initially, we probably do know what the device will look like, and we often do not know too many details associated with the specifications. The design concept phase will drive and determine many of the device–protocol design and performance specifications required for the particular applications and operating environments under consideration.

6.4.1.1 Patient Considerations and Constraints

The electrotherapeutic device design effort requires a considerable amount of time and effort to deal with human engineering issues. And the electrotherapeutic device designer must consider the needs of the health care practitioner who may be administering treatment in a clinic or hospital, along with the patient who may be using the same device at home in the self-administering mode.

A number of electrotherapeutic devices that have been used in the treatment of visual disease have very small numbers on their displays, small push button controls, and small control knobs. To make matters worse, the instruction sheets or manuals are often printed with small type. In this application, the user may be legally blind! Numbers and letters on the device, manuals and instruction sheets need to be large and bright so that a visually challenged person can see them.

When self-administering treatment for various forms of connective tissue disease, adhesive capsulitis, urinary tract-bladder disease, and back pain, the electrodes are often supposed to be placed in the back of the shoulder or middle of the back. And often, the patient is given just a pair of small electrodes connected to a short, coiled wire. Many older patients have problems reaching critical treatment points on the body. A long time ago, some genius came up with a back-scratcher, allowing people to get some relief in places they could not reach. Since that time, we have landed on the moon, we have (or had) little vehicles running around taking photographs and digging holes on the surface of Mars and Saturn's moon Titan, and we have developed DNA chips. Is it all that difficult to put a little of this same kind of ingenuity into electrotherapy? Why can't we design an electrical probe that will allow patients to comfortably apply electrodes anywhere on their shoulder, or back, without straining themselves or requiring assistance?

Electrotherapeutic devices must be easy to operate. Display numbers and settings must be easy to read. On-off switch controls must be clearly identified. Many people become confused when they see a 1-0 designation with an on-off switch. The patient may wonder, "Does the 0 imply an 'on' condition, or an 'off' condition? Is the 1-0 indicator inspired by the digital world, where 1 represents the 'on' state and 0 represents the 'off' state?" Also, any controls that are to be operated exclusively by the health care practitioner should not be in the patient's way, and should not even be seen by the patient when electrotherapy is being self-administered.

Health care practitioners and patients need to be able to turn the device on, place the probes in the correct locations, and push a button to start the treatment sequence. They need to have the appropriate monitoring devices and displays available to show the magnitude of the average current being delivered by the device. In some cases, impedance values and output waveform monitoring may also be useful for the health care practitioner and the patient.

From the standpoints of reliability, consistency, and therapeutic efficacy, almost as much time and effort must be allocated to the design and development of the therapeutic protocol as is allocated to the design and development of the electrotherapeutic device itself. And the development phase of the therapeutic protocol must incorporate adequate resources for documentation and the development of appropriate and complete instruction manuals.

6.4.1.2 IRB and FDA Clinical Trial Considerations and Constraints

There are a number of different types of clinical trials. Two of the more formal efforts involve an Institutional Review Board (IRB) study and Food and Drug Administration (FDA) clinical trials. An IRB is a group designated by the company or institution to review, monitor, and approve biomedical research activities that require testing on human subjects. The IRB's primary interest is to

protect the rights, health, and welfare of the human subjects, and to make sure the human subjects are properly informed. Initiating an approved rigorous IRB study effort is a very good idea before taking on the rigors of an FDA clinical trial. Clinical studies involving significant risk factors or charges will require the investigators to file an Investigational Device Exemption (IDE) with the FDA.

One of the very important items to consider in the design concept phase involves problems with double-blind studies. If the device is to be evaluated under double-blind study conditions, the device and protocol designers must address problems and constraints associated with the double-blind condition. In fact, one of the basic device and protocol design drivers that must be carefully evaluated (but which is often forgotten until the last minute) is the clinical study environment. A clinical study effort will impose significant restrictions on device controls, automated features, device decision-making capabilities, and protocol design. The clinical study environment is unforgiving with respect to any device weakness or protocol complexity. In the planning effort for clinical studies, designers should incorporate the features that are only absolutely necessary in the devices to be evaluated, and keep the protocol as simple as possible.

Electrotherapeutic devices have a significant disadvantage in comparison with pharmaceuticals in the double-blind clinical study environment. In the double-blind clinical study, neither patient nor health care practitioner can know if the patient is receiving the real treatment or a sham treatment. This is a problem for electrotherapeutic applications. Often, the patient can feel the very slight "buzz" of a microcurrent as it is being applied to a specific site (such as an eyelid). In my own experiences and observations with microcurrent devices, I have found that many patients will feel a slight buzz with an average or rms current level of 70 μA, a mild sensation at 100 μA, a slight sting at 130 μA, and definite discomfort above 160 μA. Just being able to feel the sensation when electrotherapy is applied is a problem in the double-blind clinical study environment.

If the patient feels the microcurrent, or has any sensation associated with current flow, the double-blind condition has been violated and the results cannot be included. This causes a dilemma for the device developer. For instance, the range of the most therapeutically efficacious and safe microcurrents in the treatment of visual disease often involve average, or rms, current levels between 90 and 130 μA. Most patients can feel a sensation at this range of microcurrents. What the electrotherapeutic device developer is often forced to do in a double-blind study is to reduce the current to levels that are at the edge of therapeutic efficacy, and hope for the best. In some cases, the visual acuity improvement percentages for double-blind clinical studies can decrease by a factor of two to three compared with the results achieved in controlled observational studies where higher current levels can be utilized. Since the patient in a double-blind clinical study must not feel any sensation associated with current flow; the double-blind

protocol does not allow the most therapeutically efficacious current levels to be applied. This is one of the reasons why a solid IRB observational study (with good controls) is necessary prior to any double-blind clinical trial effort. An IRB observational study has the flexibility to use current levels that can achieve high levels of therapeutic efficacy for the device and protocol. The FDA double-blind study will often constrain current levels to the lower limit of therapeutic efficacy for the device and protocol. Do not plan on the results of an FDA double-blind clinical study to represent the best performance capabilities for electrotherapeutic devices. The FDA clinical trial is an excellent tool to detect many of the basic reliability and inconsistency problems associated with the device, and can reveal many procedural difficulties associated with the protocol. As previously indicated, the FDA clinical trial will be very unforgiving with operator errors. The FDA double-blind clinical study must be regarded as a reliability and consistency evaluation tool and an opportunity to verify the lowest level of therapeutic efficacy for an electrotherapeutic device and protocol. During the FDA clinical study phase, many bugs and most of the consequences of incorporating marginal design features in the device and protocol will be highly visible.

The following performance figures may help to show the impact of the clinical testing environment on electrotherapeutic device performance results. Various studies have shown that 60% to 92% of patients respond favorably to certain forms of electrotherapy [9, 30, 31]. Limitations associated with the spectrum of patient conditions and patient population in any local area might restrict a "favorable response" to the 50% to 65% range in an observational clinical study. These are still excellent results. However, under the limitations of a double-blind study, where the patient cannot feel any sensation of current flow, the allowable current range may be so low that only 25% to 35% of the patients experience a favorable response. For an electrotherapeutic device application, the 25% to 35% results are often acceptable and are viewed as being therapeutically significant. However, before investing the time and money required for an FDA double-blind clinical trial, it would be very prudent to do a small double-blind study (with controls) during the IRB clinical study phase. This initial exploratory effort into the trials and tribulations of the double-blind clinical study environment will provide (1) useful information concerning many device/protocol reliability and consistency problems, (2) useful information on protocol steps that can go wrong, (3) an excellent way to determine the device current levels that can be used under double-blind constraints, and (4) an indication of the therapeutic response percentages that will occur with the lower current levels.

One of the most important items to consider in the device design–development plan is to utilize a device configuration that offers simplicity and ease of operation in a clinical test environment. With respect to FDA clinical trials, a simple, "dumb," and rigorously tested group of electrotherapeutic devices

should be used. Once the devices have been approved for patient use; features such as patient treatment monitoring and reporting, automated shutdown, and other automated control capabilities can be incorporated. And each feature should be added on and tested—one at a time. If all of these capabilities are incorporated too soon, reliability and consistency problems abound. Some of the most significant reliability and consistency problems in clinical testing of electrotherapeutic devices can occur due to deviations or failure of sophisticated microprocessor controls, software, and firmware.

Microprocessor control issues, software, firmware, backup power supplies, electrode/probe contact, integrity of leads and connectors, and so on, have been the source of some of the more serious reliability problems during FDA clinical trials and device applications in the field. With the combination of microprocessor control, software, and firmware, during the clinical test phase the electrotherapeutic device is often too smart for its own good, as a number of device development engineers have discovered. During the clinical study phase, the newly developed device will often make some very surprising decisions on its own that no one anticipated. Therefore, during the initial test, clinical trial, and initial market penetration, an operationally simple and relatively dumb device is much more desirable from the standpoint of reliability and consistency. Microprocessor control should be confined to basics.

Once an appropriate level of electrotherapeutic device reliability is achieved, and FDA-health care practitioner-patient confidence has been established, then higher levels of microprocessor control can be included for waveform/frequency selection, intensity control, and maintenance of performance tolerances. In addition, software and firmware can be incorporated to provide patient monitoring and feedback for the health care practitioner. But, from the standpoints of reliability and consistency, these functions should not be incorporated prematurely. I cannot say this enough, from the standpoint of clinical trials and introduction to the market place. Two of the primary electrotherapeutic device design drivers must be reliability and consistency.

With respect to electrotherapeutic devices, the costs associated with an FDA study vary, and they depend upon the skill level required, the degree of complexity involved with the therapeutic protocol, and the level of invasiveness involved with the therapy. Based on the experiences of a number of electrotherapeutic device developers, considering a dedicated, simple, and noninvasive electrotherapeutic device and protocol, the initial FDA feasibility study can require from $100,000 to $250,000 of initial setup costs per evaluation site, and approximately $1,000 to $3,000 per patient tested. A six-site double-blind clinical trial with 30 patients per site and a 2- to 4-month clinical trial length could require approximately $800,000 to $2 million of funding. Once the FDA feasibility phase of the clinical trial effort has been completed, the subsequent Pre-Market Approval (PMA) phase of the FDA clinical trials for an

electrotherapeutic device may require more than four times the amount of money spent in the feasibility phase, especially if the PMA study requires a substantial increase in patient numbers per site.

6.4.1.3 Safety Issues

Safety issues are of concern for electrotherapeutic devices at the mA and μA levels. Low-voltage dc devices can produce skin burns [32]. And as previously mentioned, 10- to 35-mA currents associated with TENS devices can produce skin burns with gel-type surface electrodes, for average current densities at or above 0.5 mA/cm^2 [4].

The 0.5-mA/cm^2 current density estimate for burn threshold appears to be somewhat conservative when current densities associated with normal physiology, endogenous wound healing, and various electrotherapeutic applications are considered. Calculations indicate that average current densities associated with vagus nerve or sciatic nerve action potentials, and accompanying ion channel activity, can vary from approximately 0.0025 mA/cm^2 to approximately 0.05 mA/cm^2. A microcurrent electrotherapeutic device delivering 120 μA to the eye for a visual disease application is delivering a current density of approximately 0.017 mA/cm^2. The current density required to support a living cell's basic metabolic rate (involving ion flow across the cell membrane) is approximately 1 mA/cm^2. A cardiac pacemaker delivering an output current pulse stimulus with a 30-μA average, using an electrode with a tip radius of 0.01 cm [33], can have a current density near the region of the electrode of approximately 95 mA/cm^2 (although the current density will rapidly decrease with distance from the electrode).

In their research on electrically induced nerve damage, Agnew and McCreery reported results for myelinated nerve fibers at different frequencies and current levels, under continuous electrical stimulation for approximately 4 hours [34]. They investigated the response of electrically stimulated myelinated nerve fibers with 3-mm diameters, utilizing frequencies at or below 50 Hz, and narrow current pulse outputs with peak output current levels of 2.5 mA or less. Under these conditions, no electrically induced damage to the nerve tissue was detected. Damage was detected for higher current levels, smaller nerve diameters, higher frequencies, and larger duty cycles. For peak current amplitudes of 2.5 to 5 mA, Agnew and McCreery [34] and McCreeery et al. [35] proposed that the electrically induced tissue damage is due to a stimulation-induced hyperactivity of individual fibers that is promoted by mass transport mechanisms, rather than toxic byproducts from electrochemical reactions occurring at electrode surfaces. Agnew and McCreery propose a significantly different nerve damage mechanism for peak current levels in the 2.5- to 5-mA range than the surface tissue burn damage reported by Patriciu et al. [4] for current levels in the 10- to 35-mA range.

Since treatment time for many electrotherapeutic applications is considerably less than 4 hours used by Agnew and McCreery, the possibility of

electrically induced nerve damage is quite low for microcurrent applications. The time factor in developing safety standards from animal standards was pointed out by Gordon et al. [36]. They indicate that the rather conservative safety standards developed from the animal study work of Agnew and McCreery cannot be extrapolated directly to human therapeutic procedures. The animal studies involved constant stimulation times that are much longer than the time frames involved in therapeutic electrical stimulation for humans.

Using Agnew and McCreery's data, Shannon developed a current-pulse duration (phase) relationship based on the ratios involving charge density [37]. Shannon indicates that his results favor minimization of electrode edge effects with an electrode configuration and geometry that has a high perimeter-to-area ratio. Recessing the electrode and flaring the opening of the recessed area has been suggested along with other more complex electrode geometries [37].

For Nordenström's NEAT-EChT electrotherapeutic cancer treatment technique, considering 25- to 30-mA currents applied to 2-cm diameter tumors, calculated current densities can have high values. However, NEAT-EChT continuous treatment times are significantly less than 4 hours, and the area where the electrodes are applied can be significantly larger than the tumor itself. Some of the NEAT-EChT current densities are significantly higher than the alleged tissue burn threshold of 0.5 mA/cm^2. Therefore, some burning activity can occur with normal tissue using NEAT-EChT. Xin has reported that Nordenström's technique must be administered carefully [38] because higher NEAT-EChT current levels can deteriorate normal tissue.

Also, for electrotherapeutic device design, with applications in the treatment of visual disease, some preliminary data taken by Toby Leonard (coauthor of [28]) indicates that there may be an upper limit for microcurrent levels used in the treatment of retinal tissue. Additional work needs to be done in this area. But it appears that as rms and average treatment current levels approach 200 μA, significant damage can occur for normal retinal cells. Some short-term wound healing and capillary absorption factors might tend to encourage higher current levels for the electrotherapeutic treatment of certain visual diseases. However, the long-term therapeutic value for visual disease may be severely compromised if normal retinal cells are destroyed by higher levels of therapeutic current. Based on the written comments from many of the nineteenth-century physicians who used electrotherapy to treat visual disease, the use of high treatment current levels may have been part of the reason for many of the inconsistent and negative results that were observed when electrotherapy was first introduced.

6.4.1.4 Legal, Copyright, and Patent Issues

Let's digress for a moment. Over the past 20 years, I have learned some very valuable lessons regarding the legal system. The bottom line appears to be: "Never, ever, place the legal system on a pedestal." Among other things, the legal

system has its own culture, logic, agendas, self-interests, points of view, biases, and language. Amazingly enough, there are times when justice is served, there are times when the right things happen. However, do not ever base your plans and hopes on an appropriate outcome when attorneys, judges, juries, and the law are involved.

In dealing with legal issues, we must remember, just because something is legal, that does not imply it is ethical. Corruption can be cloaked very effectively in legality and convoluted legalese. Also, just because a group or agency has been given a charter to be the custodian of the law, this does not guarantee that what they are doing is legal. One of the more notorious examples involves a number of State Attorney General's offices that claim "they must treat all state agencies as clients." This kind of practice violates, among other things, the principle of equity in justice and the law. In this case, when a state agency breaks the law, it has the luxury of receiving protection and guidance from the State Attorney General's office. The offending agency (or state officer) can receive advice on how to get around the law and can be represented and defended by the State Attorney General's office when the law violations are exposed. Often, State Attorney General's offices appear to engage in criminal law, protecting state agency mischief, rather than protecting the taxpayer's interests and treating all violations of the law in an equitable fashion.

In 2000, Stan Lippman, candidate for Washington State Attorney General wrote: "Contention is made that the Attorney General is compelled, under the Constitution and Statutes, to represent State officers; and therefore, the Attorney General cannot begin an action wherein State officers are defendants. Attention is called to where it is made the duty of the Attorney General to defend ALL actions against any State officer. The legitimate conclusion of such an argument is that the Attorney General must, if such a situation arise, sit supinely by and allow State officers to violate their duties and be recreant to their trusts. Instead of preventing such actions, the Attorney General often defends the delinquents."

"The law cannot be given such construction. The Attorney General's paramount duty is the protection of the interests of the people of the State. When the Attorney General is cognizant of violations of the Constitution or Statutes by a State officer, the ATTORNEY GENERAL'S DUTY IS TO OBSTRUCT THESE VIOLATIONS, AND NOT TO ASSIST; and where the interests of the public are antagonistic to those State officers, or where State officers may conflict among themselves, it is impossible and IMPROPER for the State Attorney General to defend such State officers and offices."

Read Lippman's statement in the above two paragraphs again. Recognize that his statement points out the startling facts concerning the very serious conflicts of interest embraced by organizations that have the charter to be the custodians and defenders of state laws and regulations. The position is taken where

they not only defend an officer or organization that is involved in breaking state laws, the custodians and defenders of state law may end up participating in a portion of the lawless or criminal activity on behalf of their "clients."

But the problem exists even at a higher level. The Foreign Intelligence Surveillance Act (FISA) is a U.S. law, passed by Congress, which mandates a warrant for wiretaps of U.S. citizens. Under secrecy, using 9/11 and the nation's security as a reason, President George W. Bush apparently established a secret program where the National Security Agency (NSA) could execute an end-run around FISA and obtain wiretap approval without a proper warrant. Whatever the reasons for this action, violating this law was a crime. This brings to mind a quote from former President James Madison: "I believe there are more instances of the abridgement of the freedom of the people by gradual and silent encroachments of those in power than by violent and sudden usurpation."

A former attorney wrote a letter to *U.S. News and World Report* that is even more disturbing, and blunt. He wrote [39]: "As a lawyer who is ashamed of his profession, and who has practiced law for 20 years, I believe that the abuses of the legal profession begin with the simple fact that lawyers cover up for judges and judges cover up for lawyers. The attorney and judicial grievance procedures are designed to cover up attorney and judicial misconduct, including the commission of felonies."

In any business venture or product development effort, the laws and regulations that have an effect on the business, product, or application must be well understood. And, in dealing with the law, it is important to recognize those characteristics of the legal system that are corrupt, corrupted, or corrupting.

Some laws make sense. For instance, allegedly, in Fairbanks, Alaska, it is illegal to feed alcoholic beverages to a moose. I'm not sure who would engage in such activity. However, that law appears to be reasonable when one considers the danger and damage potential that could be associated with a drunk, renegade moose. Then, there are some laws that do not seem to make any sense at all. Allegedly, in Fargo, North Dakota, you can be thrown in jail for wearing a hat while dancing. If I am Jewish, do I have to remove my yarmulke before I dance in North Dakota? If I am participating in a square dance or line dance, do I have to remove my cowboy hat? Again, I cannot write or say this enough, "Never—EVER—place the legal system on a pedestal."

Now, let's get to the point. Legal issues and litigation activity often dominate a large part of the activities associated with: (1) product design and development (failure modes must be analyzed, potential hazards must be designed out, documentation for patents and copyright must be submitted); (2) manufacturing (material toxicity problems must be avoided, the design must follow specifications, standards, and codes); (3) marketing (truth in advertising, foreign corrupt practices act); and (4) sales (antitrust laws that address collusion, price fixing, price discrimination, and so on). The semiconductor industry has often

been described as "patent hell," and the cardiac assist device industry and the pharmaceutical industry have had significant problems in "patent hell" and "reliability hell." Litigation costs associated with patents and copyright infringement, product failure, and reliability are allocated to the consumer and incorporated into the pricing strategy for almost every product on the market.

Litigation costs are also imposed by the failure modes associated with certain biomedical devices and the dangerous side effects associated with many pharmaceuticals (in truth, these are not side effects; they should really be considered as actual effects). In the December 26, 2005, (Vol. 24), issue of the *Minneapolis Star Tribune*, there was a short article stating that officials at Guidant Corporation projected that as many as 15 of every 10,000 (0.15%) of a particular implantable heart defibrillator device might fail each year, where the failure mode is associated with a short-circuit problem. It was determined that failure of this device could result in death in approximately 12% of those cases. This indicates that less than 0.018% of the implantable heart defibrillator devices sold could contribute to a death each year. The 0.018% per year death rate would seem to offer very good performance from the standpoints of reliability and safety associated with an electronic device that is the critical element of a life support system. But Guidant had to recall or issue warnings for 88,000 heart defibrillators and almost 200,000 pacemakers because of malfunctions that had occurred and two deaths that appear to be the result of the defects. Dozens of lawsuits apparently resulted from the two deaths and product recalls. Where Guidant appears to have gone wrong is that they did not report the 0.15% and 12% figures to doctors and regulators. Apparently, Guidant neglected to give proper warnings with respect to possible defects in its heart assist devices. The lack of providing proper warning labels and lack of information provided concerning failure modes have been the ruin of a number of large and small companies. Failures and unpleasant surprises will occur with any biomedical product. Some patients will experience these failures and unpleasant surprises. Without appropriate warning labels and information from the manufacturer, the charge will often be "willful negligence." Avoid that situation at all costs. Truth and candor must rule in the marketing and sales of biomedical products, and that is a tough rule to follow when one faces stiff competition.

Anticipated litigation cost estimates are often included in the cost analysis and pricing for many pharmaceutical products and biomedical devices. Many companies have to deal with the reality that their products will sometimes fail and produce a terrible result.

One of the advantages that many low-current electrotherapeutic devices enjoy is that their risk factors are very low, and their safety factors are at a very high level. In this case, the liability/litigation potential is minimal compared with other products in the health care industry. Many microcurrent electrotherapeutic devices provide output current and current density levels that

are lower than some of the local current and current density levels that occur naturally in the body. In some cases, the only way patients can injure themselves with the electrotherapeutic device is if they try to swallow it.

But where most product developers get into legal trouble is when they add features to get a competitive edge [40]. In the 1970s, when some TV manufacturers decided to incorporate an "instant-on" feature for television sets, they had to develop circuitry that actually kept the TV set on all of the time. It was a nice touch until a few of the "instant-on" sub-systems ignited, causing house fires [40]. Some loss of life occurred, and litigation costs were high.

Therefore, one of the primary legal issues that must be addressed involves product liability. To appropriately address this area, we would need another book. However, there are a number of items that stand out with respect to features that promote product liability problems.

One of the most strategically important product liability protection considerations involves proper labeling. Labels should be placed in locations that are prominent. The labels should be easy to read and the instructions should be clear. For instance, considering battery operated electrotherapeutic devices, is there any danger of a battery exploding, under any condition? The answer is "yes" for certain lithium batteries (which use cobalt oxide), as some cell phone users have discovered. If the electrotherapeutic device uses lithium batteries, this fact should be displayed on a warning label and the potential hazards should be discussed in the operator's manual. Is the device small enough to put in your mouth or the mouth of a child? If the answer is "yes," a warning against possible choking or injury should be displayed on various labels. Warning labels should include a message that the device should be kept away from small children, which is something that needs to be stated for most products, even on some toys. Is there any attachment that could injure an eye or choke someone? If there is, a warning label is advisable. Has a laser device been incorporated in the electrotherapeutic system or protocol as a treatment tool, or as a recording/read-out device? If so, a warning label regarding potential damage to eyesight should be placed in a location where it can be easily seen. A number of product liability problems have occurred for companies that placed warning labels or warning messages in locations or in documents where the warning messages were not easy to see or not obvious.

Labels, safety guards, and appropriate instructions fall under the category of foreseeable use and misuse (both intentional and unintentional). Before a product is made available to the public, the designer and manufacturer must spend a considerable amount of time evaluating every possibility associated with misuse or abuse of the product. In many cases, a warning label is not considered complete if the consequences of misuse and abuse of the product are not clearly identified.

Once product liability issues are defined during the design concept phase and (hopefully) designed out as the concept takes form, patent and copyright issues, documentation, and procedures will require a considerable amount of time and effort. Patent law and copyright law have evolved significantly. Copyright protection is more immediate, and less complicated to acquire, than patent protection. Initial copyright protection in the United States begins the moment a creative work is established and fixed in some readable form or tangible medium, even if it is not officially registered in the U.S. Copyright Office [41]. In the Copyright Act of 1976, the duration of the copyright, for work created after January 1, 1978, is good for the life of the author and 50 years after his death. Even if the copyright is sold, the original owner of the copyright, or members of the owner's family, can recover or take back the copyright after a 35-year period. The Copyright Act of 1976 includes this "termination" provision [42]. However, notification to recover the copyright must be given not more than 10 years and not less than 2 years before the anticipated recovery date. A copyright can be declared for a written work. However, a copyright has more weight in a court of law with respect to infringement litigation if it is registered with the U.S. Copyright Office (http://www.copyright.gov/circs).

If a copyright suffers infringement, the general rule is that the copyright infringement lawsuit has to be filed within 3 years of the infringement. A copyright violation involving more than 10 copies and a value over $2,500 is a felony. Copyright laws are making a transition from purely civil law to criminal law. In copyright lawsuits, the "innocent until proven guilty" and "proof beyond reasonable doubt" principles are not as influential as they are in other court activity. Often, the outcome is based primarily on what evidence the judge or jury believe the most.

The basic requirement for a patent is that it must be new, useful, and nonobvious [43]. Many corporations have been accused of using patents as a method to restrain trade and minimize competition. There does appear to be some validity in this claim. A patent does exclude others from making, using, or selling a particular invention.

A patent needs to be filed within 1 year of any presentation or publication that reveals details about the invention. Also, any information given out concerning the invention immediately jeopardizes the inventor's ability to obtain a foreign patent [44]. A patent has a lifetime of approximately 20 years. However, the lifetime of the patent can be extended by repeated filings with substantive improvements or modifications. From my own experience, one of the best patent books available is *Patent It Yourself*, authored by David Pressman [45]. This book shows the various procedures, forms, and formats that must be used to submit a patent. Pressman points out that a carelessly written patent can be an invitation to infringement activity, where the patent is eventually declared

invalid in court. Between 1921 and 1973, U.S. Circuit Court judges declared almost 67% of the patents being litigated as invalid.

Litigation activity involving patent infringement can be risky for both the infringer and the owner of the patent. And filing multiple lawsuits against infringers can be very risky for the patent owner. In the case of *Mendenhall v. Astec Industries, Inc.*, involving patents on asphalt recycling for road paving, Mendenhall won in a Tennessee court. But he subsequently lost in an Iowa court. And the rule is, one loss, and you lose everything [46]. So Mendenhall appears to have "gone a bridge too far," after winning in Tennessee, and then opening himself up for a big loss in Iowa. Again keep in mind what was stated at the beginning of this subchapter, "the legal system has its own culture, logic, agendas, self-interests, points of view, biases and language."

Then, there are the various problems of ownership for inventors. Eight states (California, Delaware, Illinois, Kansas, Minnesota, North Carolina, Utah, and Washington) have preinvention assignment rights written in their labor codes. These preinvention assignment rights can impose severe restrictions and future obligations on the individuals who invent devices and processes for their employers.

In 1993, there was an attempt to designate preassignment intellectual property agreements as unfair labor practices. Preinvention assignment rights impose a variety of serious obligations on the inventor. One of those obligations requires that the inventors must assist their former employers, in situations involving the invention, for a 3- to 6-year time frame after leaving that particular employer.

The intellectual property rights issue was a real concern for me when I became involved in some part-time teaching in another state during mid-2005. The State Board of Regents employment contract was a shock to me, and I almost left in disgust on the same day I initially reported for work. According to the State Board of Regents requirements, employees essentially assign all of their intellectual property rights, for any invention or written work that has commercial value, to their state institution. The state demanded a dominant share of the financial gain from the invention or written work. And after employment is terminated, as a former employee, you are still obligated to assist the state institution in any activities associated with the invention, for the rest of your life!

I found that policy to be rather strange and potentially counter-productive to an extreme. This is a state that desperately needs innovation and inventiveness to help promote economic development and the establishment of a new business base. Needless to say, I could not allow any of my biomedical/electrotherapy interests, publications, or anything that had a potential commercial value to fall under the shadow of educational institutions in that state. At that time, when I needed to work on items of commercial value, I traveled back home to do the work. Some of the students told me that their own attitude was, "Just don't

invent anything here." That kind of attitude, born out of necessity, does not bode well for any state that is trying to promote economic development and growth. Based on my own experience, and the unfortunate experiences of others who did not read that agreement carefully enough, a lot of care, analysis, and forethought is recommended for anyone who has to sign an intellectual property rights agreement. See if you can negotiate some of the harsher aspects out of the agreement. If you cannot, you may be better off going somewhere else if you have a flare for creativity.

One of the most treacherous and slippery slopes in life will be associated with any activity involving the legal system, especially the courts. The outcome of any litigation activity is often based primarily on who the judge, or jury, likes the best, and/or what kind of relationship the judge and various attorneys have had in the past. No one should ever go into a litigation activity unless they have information and a clear understanding concerning the previous relationships, political activities and social activities involving the judge, law firms and attorneys for both sides. If you can, settle out of court whenever possible—mitigate instead of litigate.

Why have I gone into such detail on this wide spectrum of legal issues? Well, it is no secret that the litigation/product liability/infringement areas involve some of the most dominant cost considerations in products and services within the health care industry. Accusations containing words such as "negligent," "incompetent," "unqualified," or "unapproved" can produce serious legal problems and expenses for any biomedical company that is a defendant in litigation activity. Legal problems have been the ruin of many good ideas, business entities, and lives. And after examining potential inaccuracies, similarities, and conflicts in many of the patents and protocols involving electrotherapeutic devices and magnetotherapeutic devices, it appears that a variety of litigation events will become very expensive and time-consuming for various individuals and companies involved in these technologies. The frequency of these "events" will increase as FDA (U.S.) and CE Mark (European) approvals are obtained, as the worldwide addressable market opens up, as larger companies become involved, and as the revenue potential increases.

A few years ago, I was being interviewed by the management of a semiconductor company who were considering hiring outside talent for some of their product planning and forecasting efforts. One of the people interviewing me seemed very preoccupied and agitated. In fact, he really did not interview me. He just needed to talk to someone, outside the company, who was willing to listen. As I recall, just before I left his office, one of the last statements he made to me was, "Please forgive my whining, George. But I can't help it. I hope people like you can come up with ideas to help us get out of this litigation curse that we constantly have to live with. Day after day, nothing but lawsuit this and lawsuit that. It would be nice to just do some normal business for just one month

without going to court with some ##!!** competitor who has nothing to complain about, but just wants to get in our way and keep us out of the marketplace. And George, let me tell you, justice seldom prevails. The best liar wins." He paused, so I asked, "Did you say lawyer or liar?" He smiled slightly and said, "I will leave that up to your imagination." As I left his office, I began to realize that the level of bias, corruption, and distortion in the legal system had gone beyond all reasonable boundaries. Because the man who was revealing all of this to me was a corporate attorney.

6.4.1.5 Codes and Standards

The National Electric Code, in the National Fire Protection Association NFPA 70 document, has been developed to safeguard people and property from electrical hazards. Factory Mutual (FM) and Underwriters Laboratory (UL) have developed standards to determine if an electrical device is intrinsically safe. One might think that a small battery operated device would not be hazardous. That kind of thinking is the fodder of lawsuits. Certain types of batteries can explode, battery chargers can become hot enough to cause first-degree burns, and pumping gas when a cell phone call occurs has resulted in a few spectacular fires.

There are a variety of laws regulating biomedical device development including Medical Device Reporting regulations and the Safe Medical Devices Act of 1990. The American Society for Testing and Materials International (ASTM) has developed standards for medical and surgical devices. If any part of the biomedical device comes in contact with the patient, ASTM reports and activities involving standards of cleanliness for certain types of biomedical devices (surgical devices and implantable devices) might provide some very good goal setting tools.

The FDA and the European Union have their Quality System Regulation requirements for medical device design, product development and manufacturing.

6.4.2 Some Aspects of the Continuing Design Process

Volumes could be written on topics relevant to the continuing design process. We will address just a few critical issues here.

Keep in mind that one of the continuing elements of device design and protocol design involves documentation. It is very apparent when a manufacturer addresses the documentation phase at the last minute, or after the device/protocol design and development work have been done. Under these conditions, the documentation is usually incomplete, difficult to understand, and sloppy. Operating and maintenance documentation for electrotherapeutic devices and protocols should be an ongoing concern in the continuing design

process. At the very minimum, operating manuals should include information on:

1. Appropriate treatment current levels and safety limits;
2. Current versus impedance characteristics (with some information on how much variability exists in that characteristic from one device to another);
3. Frequency settings (if done manually) or frequencies covered and/or frequency range covered if the frequencies are selected automatically;
4. Clear and informative drawings or photographs of probe placement for various health problems;
5. Ttime duration for each component in the treatment protocol;
6. Specifics on care and placement of electrodes;
7. Simple trouble-shooting techniques for easily correctable malfunctions;
8. An explanation (with pictures) for each control and battery replacement;
9. Meaning of display information;
10. Description of items controlled by firmware;
11. An overview of the art and science behind the electrotherapeutic treatment device and protocol including references from scientific journals, medical journals, and health magazines.

From the standpoint of the person administering the treatment and the patient; protocol steps, operating directions, and explanations should be straightforward, simple, and within reason. An interesting article appeared in the November 1974 issue of the *Ohio State Engineer* on this very subject. The focus and recommendation of the article was "eschew obfuscation," or "avoid making things obscure or confusing"; and more simply stated: "keep it simple."

They gave a great example. Suppose a group of people want to express a mathematical point. The person who is really focused and rigorously trained in the area of interest might write out the following:

$$\ln\left[\lim_{z\to\infty}\left(1+z^{-1}\right)^{z}\right]+\left(\sin^{2}x+\cos^{2}x\right)= \sum_{n=0}^{\infty}\cosh y\left(1-\tanh^{2}y\right)/2^{n} \tag{6.1}$$

Then, another math wizard comes along and says, "Oh, that is much too complicated. This is the mathematical relationship you are trying to communicate, in much simpler terms."

$$\ln e + \left(\sin^2 x + \cos^2 x\right) = \sum_{n=0}^{\infty} 1/2^n \tag{6.2}$$

"Oh, yes, that is much simpler. But what does it mean?" So another, more applications-oriented person comes along and says, "Here is what it means":

$$1 + 1 = 2 \tag{6.3}$$

There are many methods one can use to describe or explain relationships and ideas. Some methods show the information in a format that is easy to understand. Other methods show the information in ways that are impossible to understand. When writing operating manuals and documentation for manufacturing, keep this thought in mind, "eschew obfuscation."

6.4.2.1 Probe-Electrode Design Considerations

Electrotherapeutic device probe-electrode components often produce some of the most serious design deficiencies that impact electrotherapeutic device applications. One of the more effective electrodes for visual disease and wound healing applications is the combination of a cotton-gauze tip with a saline solution. In many wound healing applications, saline drenched gauze dressings serve as wound site electrodes.

Gelled cotton-gauze in hollow metal tips offers a relatively convenient and comfortable electrode configuration. Preparing them can be a bit messy, and the metal tip that contains the wet cotton-gauze material can become corroded and clogged with residue if not cleaned periodically. However, with cotton-gauze and saline solution, there is no problem with chemical dissociation of metal electrode material into tissue. All metals chemically dissociate, even platinum. Some people are allergic to certain metals, and many of them suffer severe skin rashes when exposed to nickel in steel and silver, or copper from brass.

The saline-dripped cotton-gauze tip tends to provide a consistent contact over long treatment times. Any gel that is coated on a metal electrode dries out quickly. Significant patient discomfort can occur as the gel on a metal tip dries and the active area of the metal probe-tissue contact decreases as a result of the gel drying.

Rose and Roblee [47] provide data indicating that charge densities of 20 to 50 $\mu C/cm^2$ can produce chemical dissociation of platinum into surrounding tissue. Lyte, Gannon, and O'Clock [27] noticed chemical corrosion of platinum

electrodes immersed in media, and dendrite growth on the electrode surfaces, at current levels of approximately 15 μA over time frames of approximately 10 hours. Considering a NEAT-EChT current of 60 to 70 mA applied to a 2-cm diameter tumor for several hours, using platinum electrodes, chemical dissociation does occur for this particular therapeutic modality.

Simulation studies strongly indicate that the probe-electrolyte-tissue interface is quite complex and is responsible for some of the very unusual waveform variations observed that are associated with the cascaded series of elements in the conductive pathway, including: (1) the movable electrode probe tip-gel interface; (2) gel-tissue interface; (3) tissue in the conductive pathway; (4) tissue-gel interface at the counterelectrode; and (5) the gel-counterelectrode probe tip. Simulation results shown in Chapter 7 provide some unique views of the electrotherapeutic waveform at various interface locations, and can help to explain some of the inconsistencies and distortion problems observed with electrotherapeutic device waveforms.

6.4.2.2 Design Review: Ignore at Your Own Risk

Some of the most tragic examples of engineering failure and engineering disasters occurred because of various failures to address important issues during the engineering design review process. The collapse of the Quebec Bridge in 1907 was, to a large degree, the result of a failure to question the exaggerated self-confidence of the chief consulting engineer. He did not adequately consider stresses on the bridge compression members, even as those members started showing signs of buckling two and a half months earlier. A bridge builder's hubris went unchecked, and 75 men were crushed as the bridge collapsed [48]. In January of 1986, NASA's "hubris" produced a sequence of oversights that finally resulted in the Challenger disaster [49] due to, among other things, breached O-rings. What is very disturbing about the Challenger disaster is that the breached O-ring problem was defined, discussed (with warnings), and ignored in a number of design reviews. To make matters worse, none of this information was officially relayed to the NASA managers who had the authority to cancel the flight.

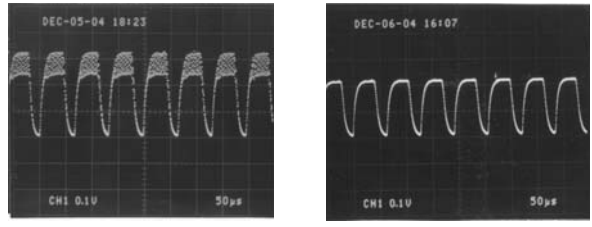
6.4.2.3 Reliability, Consistency, and Quality Control Issues

A substantial amount of literature concerning the development and application of the first generation of electrotherapeutic devices during the early to late 1800s indicates that if anyone has (1) a selection of wet cells or dry cells (batteries), (2) resistors, (3) metal probes, (4) switches, (5) control knobs, (6) a container, and (7) a soldering iron, they have the basic components and tools to develop electrotherapeutic devices for applications in wound healing, cancer, visual disease, blood pressure reduction, fracture healing, infections, neurological disorders, and connective tissue disease. In addition, this resource base would be enough to produce a modest amount of therapeutic efficacy. But this simple

approach would be plagued with consistency, reliability, and quality control problems. The electrotherapeutic operating environment, conditions, and constraints are highly variable. Variability associated with patient tissue impedance, current output (short term and long term), power supply output, deteriorating circuit interconnections, improper settings and adjustments, abuse from the user, protocol variations, and probe contact quality can cause significant consistency and reliability problems with respect to therapeutic efficacy. However, this limited level of sophistication and simple approach for the first generation of electrotherapeutic devices did provide some positive results.

As the more sophisticated second generation of electrotherapeutic devices were introduced, reliability and consistency improved. However, the addition of other electrotherapeutic device output parameters such as waveform structure and frequency added more complexity to electrotherapeutic protocols. Quality control issues became more serious. Some of the devices required more sensitive electrical and mechanical parts, which were more subject to degraded performance or deterioration from wear and tear, lack of maintenance, or improper calibration and testing procedures.

Figure 6.3 shows one of the more serious quality control problems that can occur if electrotherapeutic devices are not properly calibrated and tested at the end of each production run. The two photographs show output waveforms for the same type of device, where each device was manufactured in a different production run. The first photograph [Figure 6.3(a)] is the correct waveform structure for one device delivering current to a resistive load. The second photograph [Figure 6.3(b)] shows the waveform for the same device model, obtained from a different production run. Notice, the top structure of the waveform for the second device is missing. This can occur due to errors in component placement, cold solder joints, improper solder techniques, and cracks in printed circuit boards and substrates.



(a) (b)

Figure 6.3 Photographs of output waveforms for the same electrotherapeutic device obtained from two different production runs. The high-frequency waveform that is superimposed on the somewhat distorted rectangular carrier wave for (a) the first unit is missing in (b) the second unit. This missing waveform component is indicative of a serious quality control problem in the manufacturing process.

The electrotherapeutic device associated with Figure 6.3 exhibited consistency and reliability problems when applied to patient tissue. For some of the devices tested, there was no time-varying output waveform, only a low dc output was observed and measured. When the device did work, the output waveform exhibited significant waveform distortion and variations in distortion for different patient tissue loads.

Information obtained from some electrotherapeutic device manufacturers show pronounced spikes on the leading and trailing edges of their output waveform. The incorporation of these spikes are attributed to waveform design. However, when the output signal port for some of these electrotherapeutic devices is coupled into a resistive load, the output waveform may not have any leading or trailing edge spikes. For most of the conventional microcurrent devices, the leading and trailing edge spikes are actually associated with the resulting current waveform, and they are due to the effects of resistance and capacitance at the wet or gelled electrode-tissue interface. The spikes exhibit significant variations over time, and from patient to patient. This waveform spike effect can be modeled, and the results are shown in Chapter 7. For some electrotherapeutic devices, the waveform advertised appears not to be the outcome of intentional design, but seems to be the result of an interaction with the impedance (involving resistances and capacitances) associated with the electrode-electrolyte-tissue system and its various interfaces.

6.5 Summary

The steps in an engineering design process often involve: (1) recognizing a need, (2) defining the problem, (3) gathering the information, (4) conceptualizing alternative approaches, (5) evaluating the alternatives, (6) planning the project, (7) selecting the preferred alternative, (8) communicating the design, and (9) implementing the preferred design. Designing a therapeutic device and protocol will also require a significant amount of time and effort in the analysis of safety, reliability, and consistency considerations along with the clinical test environment. As the device starts to take form, manufacturing requirements and capabilities must be included in each phase of the design and development effort.

In design classes, the "design concept" tasks are often used and defined incorrectly. A design concept does not initially concentrate on the thing or item being designed. A design concept involves a large part of the beginning of the design process, and it often requires much more thought and structure concerning operating environments, tasks that the item is supposed to perform, cost and manufacturing considerations, clinical test constraints, legal and patent issues, addressable and available markets, and time limitations.

Once the design concept issues are evaluated, the electrotherapeutic device designer must begin to consider device operating characteristics such as current and voltage characteristics as a function of varying patient impedances, frequency choices, and waveform design considerations. Design drivers associated with each therapeutic protocol must be considered.

Preproduction devices that are scheduled to be used in clinical trials should not be allowed to make too many decisions, other than enforcing output current maximum values. Hardware, firmware, software, auxiliary backup power, lithium batteries, and so on, can produce all kinds of reliability problems during initial clinical trials and field testing. Initial clinical trials and field testing should be done with relatively uncomplicated and dumb devices. Once the basic testing and approval phases are completed, then the additional monitoring, decision-making, and controls can be added to the electrotherapeutic device.

In each design phase, the weak links associated with electrotherapeutic devices and systems must be continuously anticipated and evaluated including the probe-tissue interface, device reliability, quality control issues, device control and decision making problems, human engineering considerations, instruction manuals and customer service, and follow-up for operating problems and intermittent failures.

From the information presented in this chapter, along with some of the material in Chapters 4 and 5, there might be an implication that design is restricted to engineering. At this point, the reader could have the impression that scientists do not participate in design activity. This impression would give a rather incomplete picture of science. Scientists are required to design complex experimental procedures and protocols. They often have to design their own measuring and monitoring equipment because the equipment they often need is not commercially available. But two of the primary differences between science and engineering involve the elements of time and immediate action.

Dr. Lyle Feisel, dean emeritus of the Thomas J. Watson School of Engineering, SUNY, Binghamton, New York, provided an excellent overview of the basic differences between science and engineering in the Spring 2006 issue of the publication, *The Bent of Tau Beta Pi* [50]. He writes, "Engineers, whose job it is to harness nature, are required to take action, while scientists, whose task is to understand nature, are not required to take action." "Scientists can just keep pecking away, approaching an answer asymptotically. Nature isn't going anywhere. But engineers have no such luxury. In the design process, engineers have to make assumptions, linearize the nonlinear, estimate quantities that we are not able to measure, and then—do something. Engineers have to do something—even if it might be wrong."

In 1973, I coauthored a paper in *Applied Physics Letters* with Mike Duffy (formerly with RCA Princeton Research Labs) on the properties of AlN and GaN thin film surface acoustic wave structures for signal processing

applications. Other papers published on the same subject did not agree with the data we presented. In 2005, 32 years later, a paper was published that confirmed the measurements we made in 1973, and verified the validity of the technique we used. It took 32 years to confirm and finally, verify, our results. That is science.

Not long before I started writing this book, I was asked to participate with a design team involved in the development of a biomedical device. A design effort for this device had been ongoing for a year and a half. But, the original design approach and protocol were not working at all. Most of the previous work was useless, and the whole process had to start again from ground zero. Also, most of the money had been spent on the original effort that did not work. The new device had to be designed, fabricated, tested, and put into production in less than 6 months on a very limited budget. That is engineering.

When I am in the mood for comfort and deep pondering thoughts, my choice is science. When I am in the mood for excitement, stress, doing the best I can with what I have, and shooting for the moon, my choice is engineering.

Exercises

1. During a number of research and development efforts, I have often heard one of the participants say, "the devil is in the assumptions." How does that statement relate to the first six chapters of this book?
2. Let us assume that an inventor submitted a patent for a device with claims involving features that are obvious in view of prior art. The inventor knows that the technology and the device are based on technology and techniques that are already available. Also, the patent copies some of the frequency settings and protocols mentioned in other patents. The inventor paid a patent attorney to perform due diligence and put the patent into the proper format for submission. The patent has just been approved and granted by the patent office. Do you anticipate any potential problems for the patent holder? Explain.
3. Assume a NEAT-EChT device inventor based his patent claims on the destructive effects of pH on the tumor being treated. All of the claims are focused on the effect of the applied current on extracellular pH, with extracellular pH described as the primary entity in tumor destruction. The patent holder sues another company for patent infringement. From what you have read, who do you think has the most significant problem here, the patent holder or the infringer?
4. The statement was made in this chapter that "many corporations have been accused of using patents as a method to restrain trade and

minimize competition." Has there been any effort to restrict this kind of activity?"

5. From the first six chapters, itemize some of the research results that influence the safety aspect concerning average output current levels.

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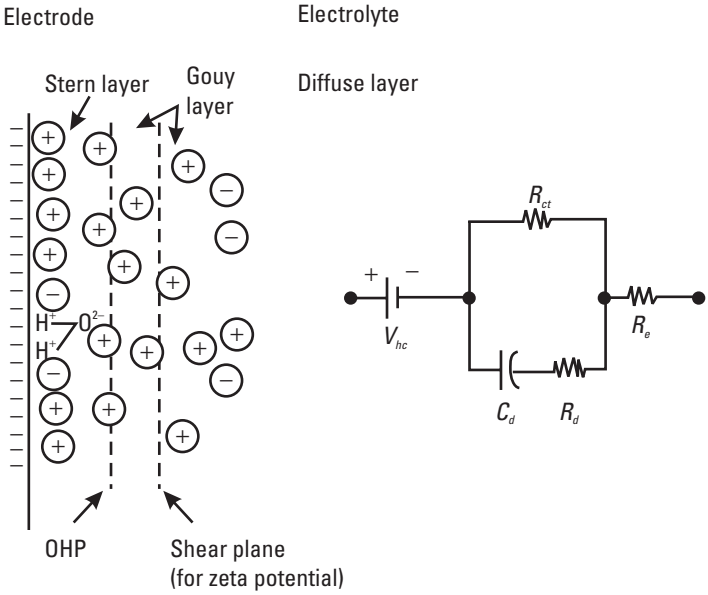
7

Simulation Results: Theoretical Performance Compared with Actual Performance

7.1 Electrode-Electrolyte-Tissue Interface Issues

A paper authored by Wilson Greatbach provides some interesting insights into the electrode/electrolyte interface associated with a contact electrode [1]. Greatbach describes a polarizable metallic electrode, in an electrolyte, as an ion collector, where "ions accumulate in a diffuse layer within a micron of the surface of the metal." In this case, there is very little current that flows across the electrode-electrolyte interface until a certain voltage is exceeded. Until that voltage is reached, each incremental voltage increase produces a higher potential gradient in the electrolyte, attracting more ions to the surface of the metal [1]. The increasing ion concentration produces a surface electric charge on the electrode, as shown in Figure 7.1.

With a very small current flow across the electrode-electrolyte interface, the space between the electrode surface and surrounding ions acts as a leaky capacitor. Greatbach provides swept waveforms indicating a rectification process is occurring at the electrode-electrolyte interface for certain metals. He indicates that nodal and/or cathodal corrosion processes appear to contribute to the rectification properties. McAdams and Jossinet discuss the onset of electrode-electrolyte interface impedance nonlinearities that are due to variations in current density and phase angle of the polarization impedance with applied frequency [2].



Electrode-eletrolyte interface showing outer layer Helmholtz plane (OHP) where most of polarization layer potential drop occurs and the diffuse layer

(a)

Electrode-eletrolyte equivalent circuit showing half-cell potential (V_{hc}), charge transfer resistance (R_{ct}), double layer capacitance and resistance (C_d and R_d) and electrolyte resistance

(b)

Figure 7.1 (a, b) Simplified diagram and equivalent circuit for a polarized electrode in an electrolyte solution showing a double layer of electrons and ions (Helmholtz layer) and a diffuse layer of ions.

Geddes et al. indicate that an electrode-electrolyte interface can be characterized by four components: a half-cell potential, resistance, capacitance, and a current dependent leaky diode (at very high sinusoidal current densities) [3]. Geddes [4], Thomasset [5], Franks et al. [6], Carter et al. [7], Poletto and Van Doren [8], and Kolen [9] provide a number of equivalent circuit possibilities and conditions to model and simulate the interfaces between the electrode, electrolyte, and tissue for electrotherapeutic applications. From the standpoint of current density, Geddes points out that the higher current density values are generally associated with the perimeter of the electrode that is in contact with an electrolyte [3]. In my own experience, not long after initial application, the conductive solution or gel is often pushed out toward the edges of the electrode. As the conductive solution or gel moves out, the relatively dry or nongelled metal surface of the electrode makes nonuniform contact with tissue. When this occurs, even the lower therapeutic current levels (less than 100 μA) can become

very uncomfortable due to the high current densities at the small nonuniform contact points between the electrode and the tissue. Also, significant skin irritation can occur with higher levels of electrode chemical dissociation as the solution or gel moves or dries out. Chemical dissociation of the electrode material does occur at the tissue-electrode interface. This effect is particularly bothersome because some patients are allergic to certain metal constituents in electrode probes that are used in therapeutic applications.

The electrode-electrolyte-tissue interfaces appear to contribute to some of the more confusing and misunderstood design parameter issues for electrotherapeutic device development efforts. It is very important to recognize that the source voltage waveforms observed on an oscilloscope display may have a significantly different structure compared with the current waveform that is associated with tissue. It is important to spend some time in this area and analyze the different waveforms observed at specific points in electrode-tissue interfaces, or tissues, that are derived from the same basic source waveform.

Some electrotherapeutic device claims are based on unique, proprietary, or patentable waveforms. Often, the "unique" part of the waveform (i.e., spikes in response waveforms) seems to be the result of a transient effect. In many cases, the transient effects associated with the response waveforms are highly dependent upon the probe-electrolyte-tissue load and are not consistent operating characteristics incorporated as a result of rigorous electrotherapeutic device design.

Therefore, it would appear that the design-development effort for any electrotherapeutic device would benefit from a device input/output simulation. This will help to properly characterize the highly variable interface between the electrode, the electrolyte, and patient tissue and evaluate their effects on output waveforms and output levels. Before the device development and manufacturing phases take place, the detection of mistakes and design flaws with the use of computer simulations can help to avoid serious penalties in cost, time, and potential litigation if the flaws are discovered in the simulation effort before the devices are being clinically tested, manufactured, and sold.

7.2 Simulation Studies: A Critical Part of Any Electrotherapeutic Device Design Process

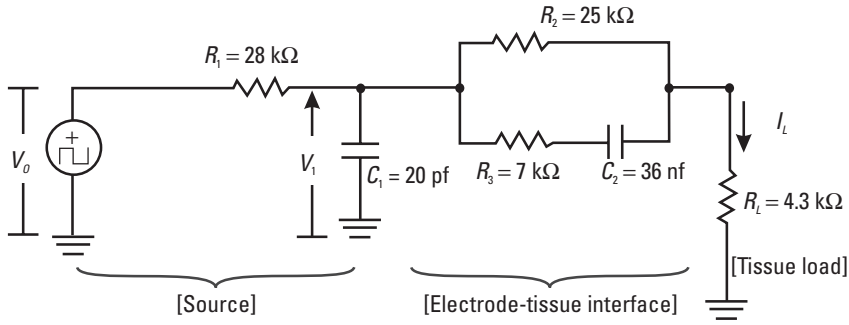
One of the first steps in determining the effect of the electrode-electrolyte-tissue interfaces on waveform and current output might be to simulate the electrotherapeutic device as a constant current source and as a constant voltage source, with a connector/wiring capacitance at the device output port, an R-C network model for the electrolyte-electrode interface, and a simple resistance or resistance-capacitance combination for the patient tissue load. This approach should produce the kind of output response waveforms (current and voltage)

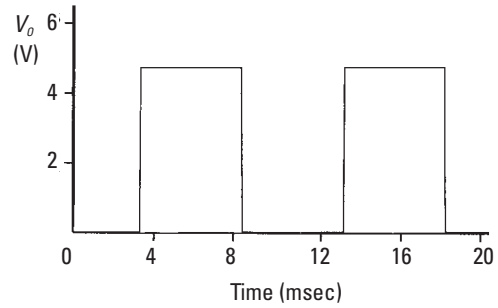
that appear in a variety of published papers and operating manuals concerning electrode-tissue and electrode-electrolyte response characteristics. I often use multiSIM–Electronics Workbench simulation tools simply because they have been the easiest for me to figure out and apply. My computer skills are somewhat primitive, so I normally use computer software that provides the most readable menu, clearest icons and best instruction manual.

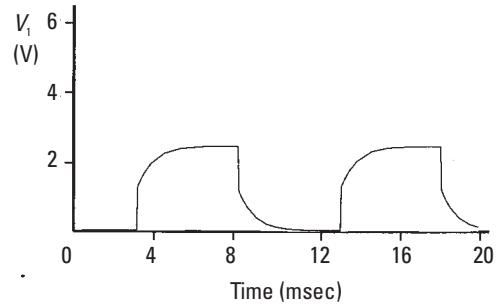
Figure 7.2 shows the simulation results for a simplified model of the electrotherapeutic device source, electrode-electrolyte interface and tissue impedance. The current-voltage response waveforms are shown for a square wave signal source with various resistance-capacitance (R-C) and resistance-impedance elements. Although the electrotherapeutic device is not an ideal current source, the source output series impedance will serve as a current limiter. With this feature, the output current will not vary significantly with relatively small changes in load impedance. The electrotherapeutic device source output, V_O, is a rectangular waveform with sharp edges at the leading and trailing edges. The voltage waveform at the electrode, V_1, for the constant current source approximation, is the result of V_O being filtered by the load. Although it makes an abrupt initial increase, V_1 is rounded at its leading and trailing edges, and is no longer rectangular in shape.

Voltage, V_1, rises abruptly with V_O because the capacitor, C_2, is initially uncharged. The equivalent resistance of the parallel R-C circuit at that first instant is 5.47 kΩ. V_1 is the result of the voltage divider circuit involving a total of the combination of the 5.47-kΩ resistance and 4.3-kΩ resistance in series with the 28-kΩ source resistance and V_O, resulting in an abrupt increase from 0V to 1.3V [V_1 = (5V) (9.77 kΩ / 37.77 kΩ) = 1.3V]. However, once the capacitor charges up to its maximum value (it takes just a few milliseconds to do this), the circuit branch with the 7-kΩ resistance and the capacitor acts like an open circuit, and the 5.46-kΩ value is now increased to 25 kΩ. The voltage divider circuit ratio is now increased and the peak output voltage for V_1 increases to 2.56V over the interval of a few milliseconds [V_1 = (5V) (29.3 kΩ / 57.3 kΩ) = 2.56V]. Figure 7.3 shows actual voltage waveforms, similar to the simulated waveforms of Figure 7.2, for a high impedance electrotherapeutic device being used to treat an ankle injury. Figure 7.3(a) shows the device output waveform, V_O. Figure 7.3(b) shows the voltage waveform at the electrode, V_1, for one point on the ankle. Notice the similarity between the actual voltage waveform, V_1, in Figure 7.3 and the simulated waveform, V_1, in Figure 7.2. One can see that the relatively simple equivalent circuit used provides a reasonably good simulation for the kind of waveforms one can expect with the application of rectangular device output waveforms to electrode-tissue combinations.

With respect to the output current waveform, current overshoot spikes occur at the leading and trailing edges of the waveform, as is indicated by the







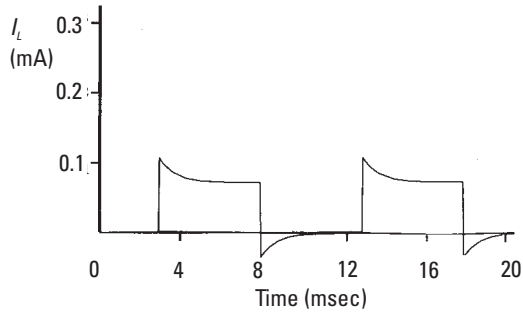
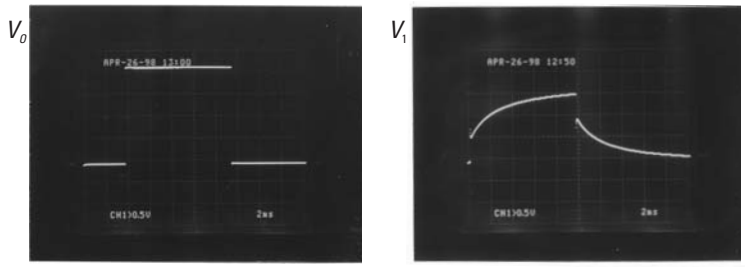


Figure 7.2 Simulated voltage and current waveforms for a relatively high impedance electrotherapeutic source that provides a rectangular wave output, V_0, for the electrode-tissue system. Notice that the voltage waveform associated with the electrode and electrode-tissue interface, V_1, and the waveform associated with current, I_L, have significantly different waveshapes compared with V_0.

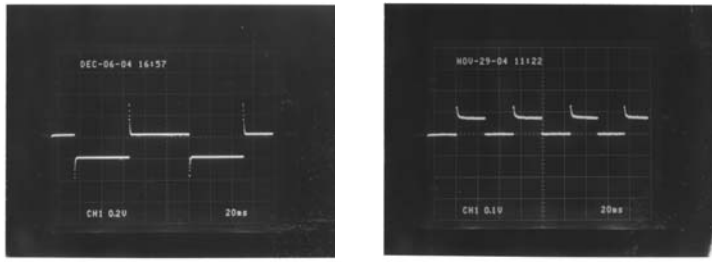


(a) (b)

Figure 7.3 (a, b) Electrotherapeutic device output waveform, V_0, and waveform at the electrode, V_1, for an application involving an ankle injury. Notice the similarity between the voltage waveforms in this figure with the voltage waveforms of Figure 7.2.

simulation in Figure 7.2. Figure 7.4 shows current overshoot spikes that occur with two different electrotherapeutic devices that have rectangular output waveforms. The reason the current waveform has spikes on the leading and trailing edge is because the electrode-tissue interface circuit acts as an approximate differentiator. For instance, just focusing on the capacitor, we know that the current through a capacitor, i_C, involves the time differential of the voltage applied to the capacitor:

$$i_C = (C)\, dV_C / dt \tag{7.1}$$



(a) (b)

Figure 7.4 (a, b) Current waveforms (with spikes) for two different electrotherapeutic devices. The waveform in (b) incorporates an electronic circuit to restrict, or cut off, the negative polarity current spike. Both devices are operating in an approximate current source mode. The current spikes are actually higher than indicated because the oscilloscope cannot respond to the very fast risetimes for each current spike. This is due to the bandwidth limitations for the oscilloscope. So the current spike amplitudes are higher than they appear on the oscilloscope trace.

Therefore, if the voltage, V_C, has fast rise and fall times, the current at those particular instances will be a function of relatively large changes in voltage over very short periods of time, and the magnitude of dV_C/dt will be quite large. Therefore, i_C will exhibit a spike at every instant an abrupt transition occurs in the voltage waveform across the capacitor (V_C).

There is a way to reduce or eliminate the leading and trailing edge current spikes as is demonstrated by Geddes [4]. His input-output waveforms are associated with a slightly distorted source voltage pulse and electrodes connected to a patient's arm. By eliminating any abrupt leading and trailing edge source voltage pulse transitions, and rounding off the leading and trailing edges of the source voltage pulse, V_O, current overshoot spikes are not produced in the resulting current waveform in tissue. Figure 7.5 shows a simulated current waveform with no spiking. Therefore, if leading and trailing edge current spikes are desired, the structure and quality of the current response waveform will be dependent upon the rise times and fall times associated with the input waveform along with the signal generator's ability to approximate a constant current source.

Figure 7.6 shows the output waveform for a square wave signal source with a small source impedance. This approximates an ideal voltage source. In this case, the output voltage will not vary significantly with small changes in load impedance, but the output current will vary significantly. The voltage waveform at the electrode, V_1, for this implementation is very rectangular. Also, the output current waveform leading and trailing edge current overshoot is rather large compared with the current source. Clearly, from the standpoint of output waveform structure, distortion, and quality, there are significant differences in output characteristics between a current source and voltage source implementation.

The behavior of the current overshoot spike is interesting. With a low source impedance, the leading and trailing edge current spikes for the approximate voltage source are quite high. The leading and trailing edge current spikes are much lower in amplitude for the higher source impedance associated with the approximate current source. Variations in current overshoot spike amplitude, width, and area occur with changes in the various resistance and capacitance values. In Figure 7.6, the current spike time constant, τ, of approximately 0.4 ms appears to agree with the R-C product of the discharge pathway resistance (sum of 4.3 kΩ plus 7 kΩ plus 50Ω) and the 36-nf capacitance (τ = RC = (11.35 kΩ) (36 nf) = 0.409 ms).

One final thought should be given to the currents and voltages associated with the basic cell itself. Many of the old assumptions that do not consider the flow of current from the outside of the cell into the cytoplasm are highly questionable. A number of interactions between exogenously applied electric current and tissue indicate that direct and very low frequency electrical currents (primarily involving ionic flow) can have significant impacts on processes that occur in

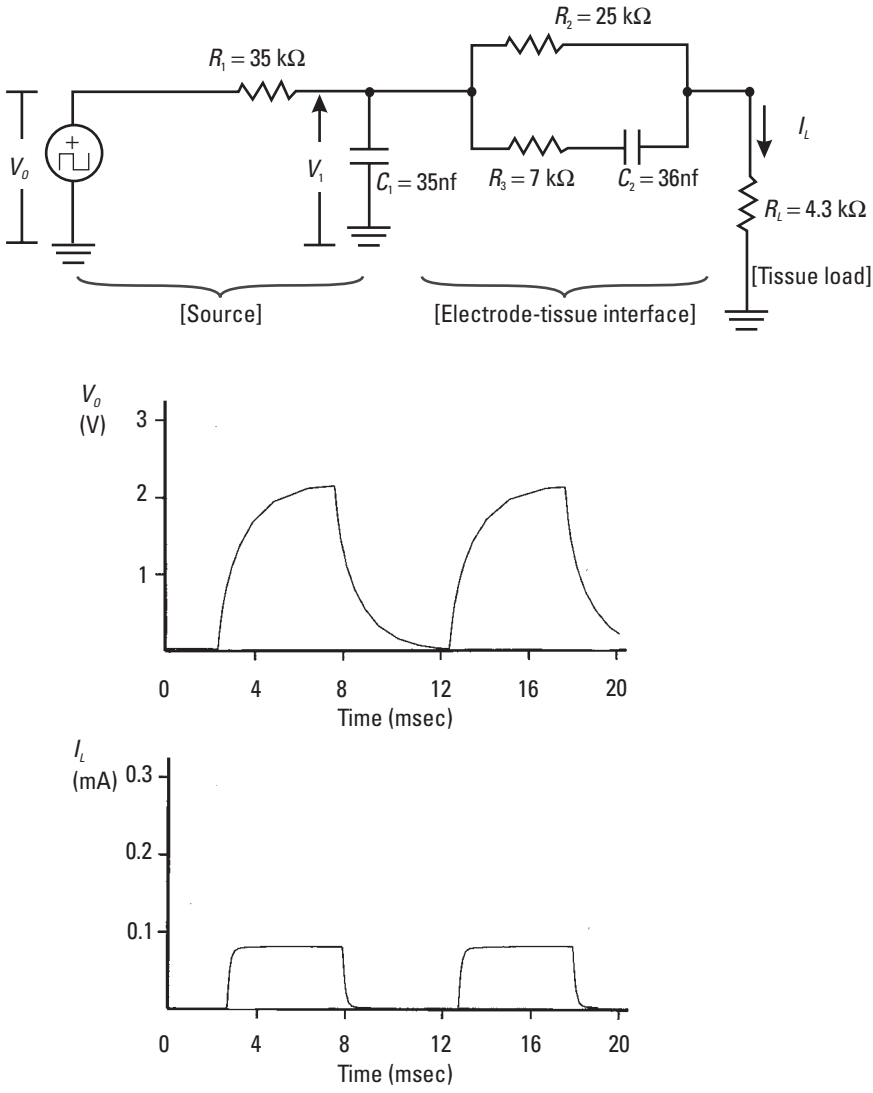


Figure 7.5 Example of the type of voltage waveform at the electrode or probe, V_1, that will produce a current waveform with no leading edge or trailing edge spiking.

cell organelles located within the cellular cytoplasm. Candidate ion transport systems could involve various cell membrane pathways including ion channels.

For the moment, we will make the oversimplified assumptions of Exercises 5 and 7 in Chapter 1. For analysis purposes, we can combine portions of the cell models that appear in Schoenbach et al. [10], Greenberg et al. [11], Sperelakis and Ramasamy [12], and Fear and Stuchly [13]. We will strip these models

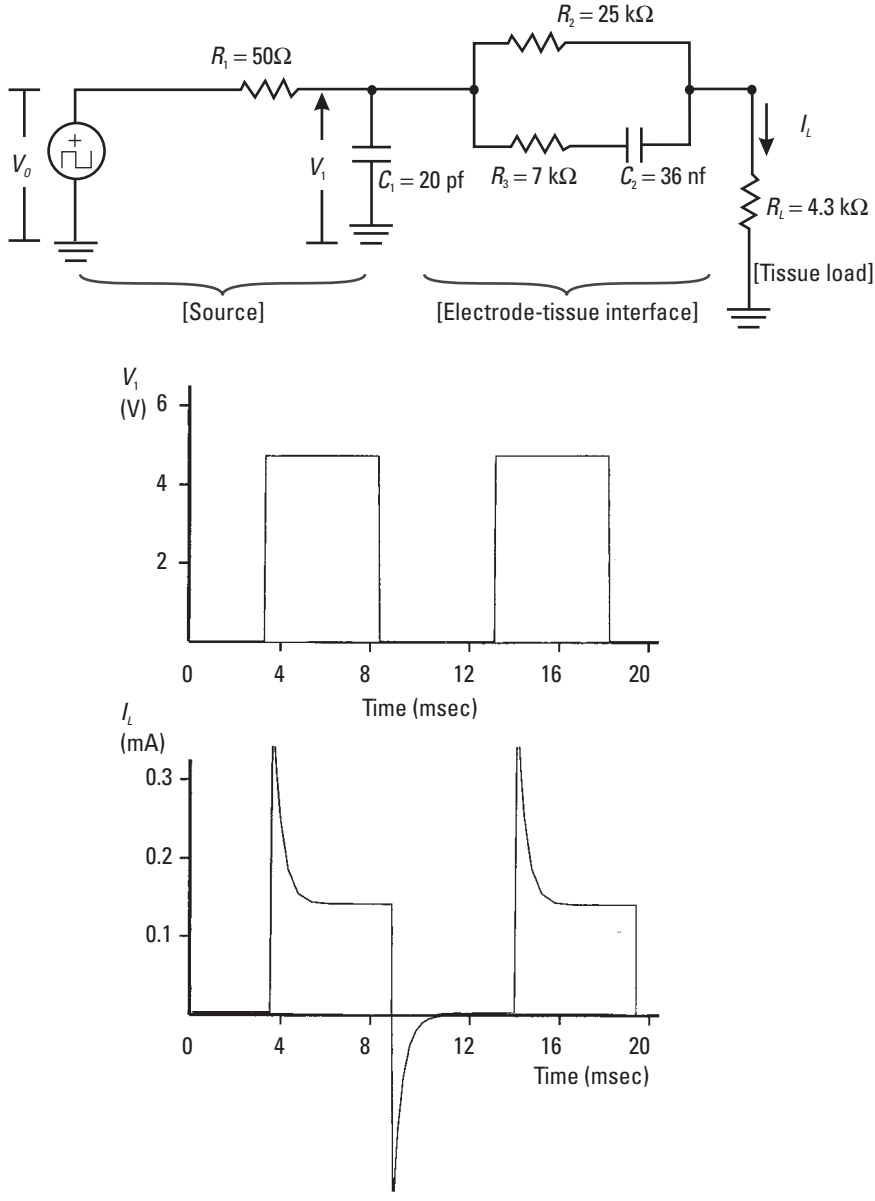


Figure 7.6 The circuit, source output voltage, V_0, electrode voltage, V_1, and the resulting current waveform, I_L, for an electrotherapeutic device set up as an approximate voltage source.

down and leave out the various membrane potential components for Na^+, K^+, Ca^{++}, Cl^-, and so on.

We will assume no gap junctions, and we will assume no gaps or interstitial spaces between the cells. With respect to ion current (hydrogen ion flow only) we will assume that the cell membrane can be modeled as a parallel equivalent circuit with a membrane capacitance of approximately 3 to 16 pf, in parallel with a membrane resistance of approximately 10 to 60 MΩ. Supposedly, on their own, cell membranes are not permeable to cations, such as H^+. But, for now, we will assume only hydrogen ions can traverse the cell membrane over a variety of pathways with electrical resistances of 10 to 60 MΩ. For good reasons, some cell biologists and biophysicists will take offense to this cell membrane model and the rationale behind it. However, the resistance assumption may not be too far off. Some cell membrane ion channel I-V characteristics exhibit slopes of 10 to 16 pA/mV, indicating local ion channel resistance values of 63 to 100 MΩ.

In order to regulate intracellular pH, every time an internal cellular chemical process uses a hydrogen ion, the ion has to be replaced. One way to accomplish this task is to transport additional hydrogen ions across the cell membrane into the cytoplasm. Since hydrogen ions participate in the production of ATP, it would be interesting to estimate how much of the cellular current might be associated with the flow of hydrogen ions across the cell plasma membrane and into the cytoplasm. Eventually, some of these hydrogen ions will reach the intermembrane spaces of various mitochondrial organelles to assist in the production of ATP.

Considering endogenously derived hydrogen ion currents, let us assume that, on the average, a person takes in 2,335 to 2,500 Cal per 24-hour day, and the person's diet consists entirely of sugar in the form of glucose (not a good idea, but it simplifies the math). At 4 Cal/g for glucose, that amounts to 625g of glucose intake per day. At 180 g/mol, 3.47 moles of glucose are taken in per day. If the total number of tissue cells in the human body is 4.6 trillion cells, the product of Avagadro's number and 3.47 mole/day, divided by the 4.6 trillion cells and the number of seconds per day, results in a total rate of glucose intake of 5.25×10^6 molecules of glucose per cell per second. Combining glycolysis and the Krebs Cycle, one glucose molecule can contribute to the production of 36 ATP molecules. The product of 5.25×10^6 molecules of glucose per cell per second and 36 ATP molecules per glucose molecule yields 189×10^6 molecules of ATP per cell per second. Three hydrogen ions are required per ATP molecule. Therefore, the hydrogen transport requirement to produce 189×10^6 molecules of ATP per cell per second would be approximately 567×10^6 hydrogen ions per cell per second. Multiplying this rate by 1.6×10^{-19} C/hydrogen ion, the required endogenous hydrogen ion current is approximately 90.7 pA, and the endogenous hydrogen ion current density is approximately 1.0 mA/cm^2. This current and current density relate to the high metabolic rate tissue cells in

the human body. Assuming passive transport through the cell membrane, this current could be associated with a hydrogen ion concentration of approximately 10^{14} ions/cm^3, at ion drift velocities of 625 mm/sec. (Should we include a small percentage of nontissue cells in these calculations?)

Considering all of the tissue cells in the human body, the endogenous current density is approximately 0.05 mA/cm^2. In this case, the 0.05 mA/cm^2-endogenous current density is an average for all cells in the body. During rest and minimal activity, approximately 4.5% of the cells in our body are engaged in relatively high metabolic rate processes (certain cells in the liver, brain and cardiovascular system). Apparently, these cells are utilizing most of the energy from the 2,335- to 2,500-Cal nutritional intake per 24-hour time period. Incorporating the 4.5% figure for the high metabolic rate cells into the calculations, the endogenous current density approaches 1.0 mA/cm^2. This is close enough for estimation purposes. The cytoplasm ionic currents for all tissue cells are in the range of 2 pA to 91 pA.

If we consider the exogenously derived current densities appropriate for malignancies, a NEAT–EChT current density of 1 mA/cm^2 has been utilized for a wide range of cancer applications. The current for an individual cell associated with this particular current density would be approximately 6 nA. Due to the vascular structure and fluid content of the tumor, approximately 4% of the total current actually reaches the malignant cells. In this case, the current applied to each malignant cell would be approximately 240 pA. Considering the simple R-C circuit model for the cell membrane, that amount of ionic current traversing a 10–100-MΩ membrane resistance would produce a localized voltage variation. A normal healthy cell would most likely be able to respond to this voltage variation and maintain its normal 70-mV membrane potential by adjusting the ionic concentrations between the exterior and interior of the cell. This could be done in the conventional cell model by the use of various pumps, ion channels, and transporters that can provide compensation. A malignant cell has a significant number of defects, poorly formed membrane structure, and a reduced membrane voltage of approximately 25 mV. With a reduced membrane voltage, the malignant cell might have some difficulties adjusting or compensating for the cell membrane voltage variation. In comparison, the localized membrane voltage, produced by the exogenous 240-pA electrotherapeutic current, might not be a drastic change for a normal healthy cell. But the larger localized membrane voltage variation, produced by the exogenous 240-pA electrotherapeutic current, could produce damaging effects on the malignant cell's structure, functions, and vitality. In vitro research and clinical studies have shown that these current and current density levels can deteriorate both normal and malignant cells, with the most serious effects occurring with malignant cells.

If cells contain cytoplasmic gels, adjustments for ionic concentration and cellular membrane voltage variations should not be difficult to achieve at the gel-membrane-interstitial fluid interfaces. The specific gelatinous state, or gel phase, is determined by a number of parameters including the extent of water structuring in the cell [14]. Differences in water structure can have an effect on proton relaxation times [15]. In cancer cells, MRI studies indicate that cytoplasmic water is less structured [14, 16, 17]. It appears that one of the differences between malignant and nonmalignant cells may involve a lower paramagnetic ion content in malignant cells making them more vulnerable to certain kinds of external stimulants [14, 17].

Also, the associated cytoplasmic gel structural changes, or phase transitions, that occur with cancer cells could make them more sensitive and less able to adjust for small variations in membrane voltage that are exogenously derived.

It is interesting to compare the analytically derived endogenous current densities with the experimentally derived exogenous current densities associated with electrotherapeutic applications. The endogenously derived current (from nutrition) was 90.7 pA per cell, with an average current density for the entire cell population of 0.05 mA/cm^2. With respect to exogenously applied therapeutic currents, the analytical results in this chapter are reasonably close with the work of Cheng et al. They provided results concerning a range of tissue currents and current densities that appear to promote the production of ATP [18]. Cheng's experimental exogenous current densities in tissue are within an order of magnitude of the previously calculated and nutritionally derived 0.05 mA/cm^2 endogenous current density. Also, the current densities utilized by Jarding [19] in his treatment protocol for macular degeneration are in the range of 0.01 to 0.017 mA/cm^2, which are quite close to the 0.05-mA/cm^2 nutritionally derived endogenous current density previously calculated. Therefore, one might expect that since the electrotherapeutic exogenous current densities are close to the nutritionally derived endogenous current densities, the exogenously applied currents from the electrotherapeutic source would have therapeutic value.

Considering the cell membrane, as we progress from the very oversimplified R-C parallel circuit to a more rigorous model, the calculations start to break down. We cannot just regard the lipid bilayer of a plasma membrane as a simple conductor with a very high resistance. The lipid bilayer of a cell plasma membrane is permeable to water and uncharged molecules, such as O_2 and CO_2. But, the cell plasma membrane is not, by itself, permeable to cations (H^+, Na^+, K^+, Ca^{++}, and so on) or anions (Cl^-, HCO_3^-, and so on). However, the cell plasma membrane utilizes a variety of plasma membrane components including ion pumps, ion channels, and transporters to transfer ions into and out of the cell. Hydrogen ions can cross the cell plasma membrane using a number of mechanisms. These mechanisms include, passage through voltage-gated proton channels (that have no apparent membrane pore), leakage in K^+ channels,

attachment to water molecules, producing hydronium ions (H_3O^+) with subsequent plasma membrane transport, and co-transport with carbohydrate molecules. Many cell plasma membranes have densities of 100 to 500 specific ion channels per μm^2 of cell membrane surface. So there appears to be more than enough ion channels available for either an endogenously or exogenously driven hydrogen ion transport task. But, not all of the hydrogen ions being transported into the cytoplasm are involved with ATP production. And, we have to ask the question: How does the transport of hydrogen into the cytoplasm continue into the intermembrane space of the mitochondria?

Several analytical problems occur with the more rigorous model when the current is divided up and transported in separate ion channels. Unless the channel resistances are enormously high, Ohm's law yields calculated channel voltages that are significantly less than the membrane voltage. As a result, the power dissipation associated with each cell is reduced, and the total power estimate for the body becomes much lower than 100W. Also, if interstitial spaces between each cell are considered, the resistance of the interstitial space is significantly lower than the resistances associated with conventional cell membrane components. In this case, most of the ion current will flow in the interstitial space and very little will enter the cell. But, any simulation involving a model of the cell will be faulty if the ion current flowing into the cell does not correlate reasonably with ATP production needs and the needs of other internal cellular chemical processes.

These apparent conflicts have bothered me for some time. From a modeling standpoint, I have a number of questions. For instance, let us start with the basic accepted cell model. Calculating the energy or power requirement for the Na^+/K^+ pumps associated with just 10% of the tissue cells in the human body, the amount of energy or power required is about 25% to 33% of the maximum levels provided by nutritional intake. Some cell biologists will agree with this 25% to 33% range (which seems awfully high to me). However, considering the additional needs for just 2% to 3% of the nontissue cells in the human body (red blood cells, white blood cells, bacteria, and so on), the energy or power requirements for their Na^+/K^+ pumps will exceed what is provided by the total nutritional intake. In other words, we wouldn't have the strength to move, eat, or reproduce with this kind of load. And, keep in mind, there are other cell membrane pumping and transport systems for various ions and molecules that require additional energy to operate. The cell membrane ionic pump model seems terribly excessive and inefficient with respect to energy requirements and cell function. From another perspective, ionic separation or partitioning at or near the cell surface has been explained by Szent-Györgyi and Ling using variations in the physical properties of structured water [14, 20]. In this case, the cellular cytoplasm has the properties of a gel that can undergo phase transitions [14], and their model requires much less energy to function.

Considering tissue impedance, the combination of the model proposed by Thomasset (Chapter 3) and Thomasset's measurements [5] appear to work very well together in explaining various segments of the tissue impedance characteristic. In Thomasset's model, the individual cells are quite close together, with a small interstitial space between them. The resistance of the small interstitial space would be orders of magnitude less than the combination of the cell membrane resistance in series with the cytoplasm resistance. This would produce a current divider effect and most of the ion current flow directed toward a cell would be diverted around the cell (path of least resistance). But, considering slowly varying electrical stimuli, a few simple calculations indicate that the cell behaves more like a combination of a hydrogen ion attractor and 10- to 60-MΩ resistor with respect to the values obtained for cell plasma membrane voltage and cellular power dissipation. Why does most of the positive hydrogen ion current appear to enter the cell? The current pathway should just go around the cell in the much lower resistance interstitial spaces. Why is each cell acting more like an attractor for distant hydrogen ions, pulling them closer and closer to the cell surface, rather than allowing the ions to travel around the cell in the interstitial space?

A strong negative cell membrane surface charge could promote an attraction for hydrogen ions. The strong surface charge could be due to the presence of negatively charged surface membrane structures in combination with a near-surface double layer of bonded or captured negative ions. So again we might ask the questions: Why is the cell behaving like a gelatinous bead, with a thin highly resistive surface film? Why does the cell behave like a gelatinous colloidal particle, with a strong negative surface charge that attracts positive ions? The answer is probably right under our noses and it may just be that the cell behaves like a gelatinous colloidal particle and proton attractor, with a thin highly resistive film at its surface because that describes just what the cell is. If that is true, a lot of cell biology dogma just went out the window.

7.3 Summary

The design-development effort for any electrotherapeutic device will receive significant benefits from a device output simulation study. This will help to properly characterize the highly variable interface between the electrode, the electrolyte, and patient tissue and evaluate their effects on output waveforms and output levels. Before the device development and manufacturing phases take place, the detection of mistakes and design flaws with the use of computer simulations can help to avoid serious penalties in cost, time, and potential litigation if the flaws are discovered in the simulation before the devices are being clinically tested, manufactured, and sold.

Very little of the total current supplied by some electrotherapeutic devices actually interacts with diseased tissue. And, under certain conditions, only a small portion of that current may interact with the diseased cell. But according to clinical, in vivo, in situ, and in vitro study results, the small amount of current that actually enters the diseased cell is more than enough to provide therapeutic benefits.

If the current models and dogma in cell biology are correct, a large part of the material in this book is reasonably accurate. If current models and dogma in cell biology are not correct, a large part of the material in this book is still reasonably accurate. What we have here is a work in progress.

Exercises

1. With respect to electrode polarization effects and electrode potential, can you find an equation for the electrode potential? Does it look familiar?
2. Compare electrode polarization effects and electrode potential with the electrical properties of colloidal particles suspended in liquid. List some similarities between the polarization effects associated with an electrode in an electrolyte and a colloidal particle suspended in liquid. What is the Zeta potential for an electrode and colloidal particle? What happens to the electrode potential as the pH of the electrolyte is decreased (more acidic)? What happens to a colloidal particle as the pH of the liquid is decreased? Why should we care?

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8

Electrotherapy Clinical Studies

8.1 The Clinical Environment

An excellent source of information that addresses many aspects of the clinical environment is the *Clinical Engineering Handbook*, edited by Joseph Dyro [1]. It is a large book and has an international flavor. Before becoming involved in a clinical environment or a clinical study, get this book and be prepared to do some heavy reading. There are some significant points in this book that should be mentioned here.

It is very apparent that if one is involved in clinical engineering details, or in the clinical engineering environment, some litigation activity must be anticipated (see Chapter 13 of Dyro's book). Increases in iatrogenic events, infringement (real or imagined), and failure to inform will enhance the probability that anyone associated with the clinical applications area will be involved in some kind of litigation and court action—most likely on the side of the defendant.

Another very interesting chapter in this book discusses clinical engineering at the bedside (Chapter 11). One of the cases mentioned concerns intermittent high-frequency noise interference in all eight channels of an EEG data acquisition system. Apparently, probe placement, equipment settings, and measurement protocol had not been a problem before. However, the reference electrode, positioned on the patient's scalp, came in contact with muscle tissue, and every time the patient felt discomfort, anxiety, frowned, or clenched his jaw, this activity would generate an EMG signal that would overwhelm the EEG signal. What is interesting from this example is that the initial assumption was made that something was wrong with the system, or that the interference was being caused by other equipment that was being used to monitor other functions. We always seem to blame the equipment. As it turned out, there was nothing wrong

with the equipment. The problem was due to an electrode that penetrated too far, producing an unexpected interaction with a region of muscle tissue that was not supposed to be part of the measurement procedure.

The details in Chapter 30 of Dyro's book concerning medical technology management practices provide some excellent information, including the importance of continually addressing improvements in patient care, maintaining high standards of care, improving quality, improving reliability and repeatability, addressing issues in utilization and cost saving, addressing risk reduction and safety issues, and improving skill levels.

Chapter 63 addresses issues associated with electromagnetic interference (EMI) in a hospital environment. In my experience, I have found the hospital environment to be one of the most prolific producers of EMI. Also, the hospital environment is one of the most sensitive environments to EMI. As an example, a cell phone can wreak havoc on surgical and intensive care monitoring equipment.

There is some excellent material on medical device research, design, manufacturing, evaluation, and control in Section VII of Dyro's book. If you intend to do any kind of research, design, development, manufacturing, implementation, or application of electric, magnetic, electromagnetic, thermal, or fluid, devices in a clinical environment, this book would be a valuable asset. But be prepared for a lot of detailed reading.

In addition, in order to get a good overview of the clinical engineering environment and clinical engineering issues, Sections 17 and 18 in *The Biomedical Engineering Handbook, Second Edition,* Vol. II, edited by Bronzino [2] are also quite informative.

8.2 Electrotherapy Clinical Studies: Wound Healing

As indicated in Chapter 1 of this book, the origins of electrotherapy in wound healing date back to the 1600s. A large amount of the information published on the application of electrotherapy to wound healing is anecdotal. However, the results have been so impressive and consistent that clinical practice guidelines issued by the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality strongly recommend electrical stimulation, or electrotherapy, as the only adjunctive therapy to enhance healing of recalcitrant and refractive pressure ulcers [3]. Chapter 1 also mentions Blue Cross of California's medical policy Number 2.02.04, which indicates that supervised use of electrical stimulation, or electrotherapy, may be considered medically necessary as a treatment for certain types of pressure ulcers (bedsores), arterial ulcers, diabetic ulcers, and venous stasis ulcers when a 30-day trial of initial wound healing management has failed.

Part of the reason that electrotherapy is such an important consideration in wound healing involves financial burdens. The medical statistics literature indicates that conventional wound healing treatment costs are very high. The cost to treat a chronic leg ulcer problem is approximately $2,500 to $3,000 per ulcer. Pressure ulcer treatment costs per patient are approximately $8,000 to $25,000. In some long-term care facilities, treatment of pressure ulcers involves over 25% of the patients. One of the most significant problems faced by the pressure ulcer patients and their health care practitioners involves infection by aerobic and anaerobic organisms [4].

The variation in healing rate for different types of wounds, utilizing currents in the 200- to 800-μA range, is interesting. Carney and Wainapel [5] report that 30 hospital patients with nonhealing ulcers were divided into two groups. One group was treated with conventional wound dressings. The other group was treated with two electrotherapy sessions per day (2 hours per session) using currents in the range of 300 to 700 μA. The group receiving electrotherapy had a 150% to 250% faster healing rate, with less pain, less infection, and a stronger scar formation in the treated areas. Wolcott et al. [6] used currents in the range of 200 to 800 μA to treat various lesions. They report a 200% to 350% faster healing rate and fewer problems with infections compared with conventional wound healing approaches. Gault and Gatens [7] reported an approximately 200% increase in healing rate, using currents in the range of 200 to 800 μA for 100 patients with ischemic skin ulcers.

A review by Hess et al. [8] describes the foundation for electrotherapy in wound healing in the work of du Bois-Reymond (1860) where he described the electrical currents (approximately 1 μA) associated with a human skin wound. Work continued into the 1940s where it was established that wounds had a positive potential with respect to surrounding uninjured tissue. Endogenous transcutaneous injury site voltages of 40 mV and current densities of approximately 22 $\mu A/cm^2$ have been associated with fingertip amputation. From the standpoint of exogenously applied direct currents for wound healing, 30-μA to 1-mA direct currents can be applied for 1 to 3 hours. High voltage (100V to 500V) applications with short pulse durations and peak currents in the 15- to 40-mA range are also mentioned. Zhao et al. indicate that electric field directed cell movements are fundamental in tissue construction and reconstruction [9]. They describe dc electric fields in regions where cell migrations occur; which include embryonic development and wound healing of skin and cornea. Endogenous and exogenous electric fields influence the migration of keratinocytes, the distribution of cell membrane receptors and the expression of epidermal growth factor receptors (EGFRs), which can all contribute to the enhancement of wound healing [9]. Zhao et al. describe all of these mechanisms occurring reasonably close to corneal injury site potentials of approximately 25 mV.

Goldman and Pollack [10] discuss the effects of 10- to 100-mV/m (RMS) electric fields, with current densities of 2 μA/cm^2 and source frequencies of 10 to 100 Hz, on fibroblasts for applications in treating leg ulcers. They report a narrow amplitude "window" between 37 mV/m and 50 V/m at 10 Hz produced enhanced fibroblast proliferation and a significant increase in normalized DNA. They also show a current density window in the range of 4 to 7 μA/cm^2 where a significant increase in normalized DNA was observed.

In a double-blind study, Vodovnik, Miklavèiè, and Serša compare the length of time to heal decubitus ulcers using conventional treatment (control group of 49 patients) and a group of 18 patients who received 2 hours of dc electrotherapy (with a treatment current of 600 μA) in addition to receiving the conventional treatment [11]. The 600-μA current was applied across the wounds using self adhesive skin electrodes. Their data indicates that, as the wound area decreased to 30% of the original size (or less), the time required to heal the remaining portion of the wound was approximately 50% longer to heal by conventional means compared with the healing times associated with combined dc electrotherapy/conventional therapy group.

For dc electrotherapy, one electrode is usually placed within the wound area, and the other electrode is placed on normal tissue at some distance from the wound site. However, there appears to be some variation with respect to the appropriate electrode polarity for certain aspects of wound healing. Chapters 2 and 3 of this book indicate that therapeutic efforts to support the endogenous wound healing process would require the placement of the positive electrode on the wound site and the negative electrode on the uninjured tissue. Well, that view is a bit of an oversimplification. Wolcott et al. presents the results of treating 75 ischemic ulcers in 67 patients, and their treatment protocol included electrode polarity reversal when a healing plateau is reached [6, 8]. Galt and Gatens reverse polarity once in their electrotherapeutic treatment protocol for wound healing [7]. Hess [8] discusses the results by Rowley et al. [12], indicating that positive polarity enhanced healing and infection, and negative polarity suppressed both. In murine studies, Denda and Kumazawa applied a negative potential of 0.5V and accelerated skin barrier recovery [13].

Sussman and Bates-Jensen [14] provide some very clear recommendations concerning polarity. They indicate that the positive electrode induces clumping of leukocytes and induces thrombosis, and this process is reversed with the application of the negative electrode to the wound site. They also mention that negative polarity, or negative current, helps to make clotted blood more soluble and minimize problems with tissue necrosis. They discuss polarity reversals as a necessary component of the various wound healing treatment protocols.

Some of the best explanations concerning the effects of the anode and cathode on necrosis, thrombosis, white blood cell accumulation, and a variety of tissue interactions can be found in Nordenström's book [15]. The photographs

that he provides for the various anodic and cathodic reactions at the cellular and tissue level are very instructive. Nordenström discusses various examples of platelet aggregation and thrombosis at the anode (positive electrode), and the absence of thrombosis at the cathode (negative electrode). He mentions the occurrence of microthrombosis in capillaries near the anode. He discusses leukocyte accumulation that can occur with both polarities. For the inflammation phase, he describes the accumulation of granulocytes in veins near the cathode. He describes how the granulocytes are repulsed by the negative electrode and accumulate in blood vessels that are near the cathode. A significant amount of this activity apparently occurs with low voltages (~2V) at 1 to 10 μA. Nordenström describes the tissue devitalization, tissue bleaching, darkening of tissue, and gas production at or near the electrodes. At 10V, there is significant gas pressure at the electrodes. The anode produces O_2 and Cl_2 gas and the cathode produces H_2 gas. The Cl_2 gas contributes significantly to the bleaching and devitalization of the tissue near the anode. Nordenström explanations provide the kind of information that shows why polarity reversals are necessary in an electrotherapeutic protocol for wound healing.

In the Sussman and Bates-Jensen book [14], a chapter by Sussman and Byl mentions the wide variety of waveforms that are available for electrotherapy in wound healing. Thorough and consistent results have been achieved in both animal studies and controlled clinical trials for high voltage pulsed current (HVPC) applications using a 100V to 150V monophasic twin peaked waveform with negative polarity (initially), during the inflammation phase) at a pulse rate of 100 to 128 pulses per second. Treatment duration is 60 minutes each day, and done five to seven times per week. During the epithelialization phase, the polarity is changed every 3 days (3 days negative, followed by 3 days positive) using a pulse rate of 64 pulses per second. In four controlled studies and three uncontrolled studies, they report a mean healing time of 9.5 weeks using these HPVC protocols.

Using an electrotherapeutic device with a high voltage (50V) pulsed twin peaked monophasic waveform, Peters et al. conducted a 40 patient randomized double-blind placebo-controlled pilot trial for the treatment of diabetic foot ulcers [16]. Patients were treated by a computer-controlled system while they slept. Healing occurred in 65% of the patients in the group treated with electrotherapy, whereas healing occurred in only 35% of patients in the placebo group. The p-value given in their hypothesis test is 0.058. The p-value represents the smallest level of significance that would lead to the rejection of the null hypothesis [17], which provides support for the statistical significance of the data.

Peters et al. [16] did not give any estimates of the resulting peak currents. However, the type of electrode mesh they used leaves the impression that the peak current levels being delivered to each patient were in the range of 25 to 50

mA, with average currents being significantly lower. The average currents quoted in some studies appear to be much too high. Depending upon localized current density levels, significant discomfort often occurs with average current levels above 0.25 mA applied for long periods of time. In order to be able to sleep during treatment, these patients would have most likely been treated with average currents lower than 0.2 mA. This would be the case if the duty cycle for the high voltage waveform was 1% or less.

A wound healing clinical study reported by Cukjati and Šavrin puts a little different twist on the choice of electrotherapeutic device waveform. They used a dc output, delivering 0.6 mA for 42 of the wounds with the positive electrode on the wound site and treatment durations in the range of 0.5 to 2 hours daily [18]. They also used a 40-Hz biphasic waveform, delivering 15- to 25-mA peak currents with a duty cycle of 1%, for 0.5 to 2 hr daily, for 181 wounds. They conducted a 214-patient clinical trial, involving 300 wound areas larger than 1 cm^2. The wounds they treated were of various types (vascular ulcerations, amputation wounds, pressure ulcers, neuropathic ulcerations, and so on). All patients received conventional treatment for their wound problems. Fifty-four wounds received the conventional treatment only. Two hundred forty-six of the wounds also received electrotherapy. Twenty-three of the wounds received the sham electrotherapy treatment. After 25 to 30 weeks of treatment, the percentage of wounds healed were essentially the same for both the biphasic waveform output device and the dc output device, and the electrotherapeutic-conventional therapy combination produced a 20% increase in proportion of wounds healed compared with conventional therapy alone. Also, within 60 weeks, over 90% of the electrically stimulated wounds healed completely while only 72% of the wounds treated with conventional techniques healed completely. The biphasic current treatment appeared to give slightly better results compared with the dc technique. Histological analysis confirmed the positive effects of biphasic current electrotherapy in areas such as improved blood circulation in the wound and surrounding tissue as well as improved post-treatment scar formation.

An area closely related to wound healing involves the treatment of various connective tissue disease problems, such as adhesive capsulitis (frozen shoulder). A woman with this condition is shown in Figure 8.1. In Figure 8.1(a), the woman has pushed her arm up as far as it can go to the point where the pain in her shoulder is very intense. You can see by the expression on her face that she is very uncomfortable. Previous to this, approximately $2,000 of X-ray and MRI diagnostics, $900 of orthopedic care, and $800 of physical therapy costs produced no specific diagnosis and no improvement in motion or pain remediation. Further treatments with cortisone and surgery were discussed. She was concerned about the problems and risks associated with cortisone shots and the kind of surgery that was suggested. Dissatisfied with the conventional allopathic medical approach, she decided to participate in a demonstration of

(a)

(b)

(c)

Figure 8.1 Treating adhesive capsulitis (frozen shoulder) using the Electro-Acuscope electrotherapeutic device. (a) Before treatment, the condition is so painful that the patient requires support for her arm. This is as far as she can move her arm without suffering severe pain or further tissue-joint damage. (b) The patient is treated with electrotherapy, while she is holding on to a counterelectrode in her left hand. Also, the treatment is somewhat relaxing and she almost fell asleep. (c) The patient after treatment, 90 minutes later—look at that smile! After the initial treatment session, her range of motion significantly improved. This was the first time in 6 months that she could raise her left hand over her head.

the Electro-Acuscope electrotherapeutic device. Her treatment protocol involved average electrical currents of approximately 100 μA, frequencies in the range of 0.2 to 240 Hz, and treatment durations of 15 minutes each for six regions on her upper body. The Electro-Acuscope electrode was placed at various points on her shoulder [Figure 8.1(b)], arm, and back. She held on to the counter-electrode with her left hand. Approximately 15 minutes into the treatment protocol, she could move her arm a bit. After 30 minutes of treatment, her arm movement and range of motion capabilities increased substantially. Figure 8.1(c) shows the results after her first treatment session. This is a photo of a very happy woman who has been given a significantly improved range of motion with a unique electrotherapeutic technique. The electrotherapy treatment reconditioned blood vessels and nerves, causing her shoulder and arm to ache for several days.

Sustained cortisone shots, frequent use of anti-inflammatory drugs, and previous surgeries can interfere with electrotherapy results for these kinds of health problems. From the results that I have seen, a follow-up treatment each year, or every other year, appears to be a good idea from the standpoint of maintaining the results achieved with the initial treatments.

8.3 Electrotherapy Clinical Studies: Diseases of the Visual System

A number of studies evaluating the effectiveness of electrotherapy in the treatment of visual disease have been conducted since the mid-1980s for retinitis pigmentosa, macular degeneration, and glaucoma. Using a combination of electrotherapy and nutritional supplementation, Michael and Allen reported improvements or stabilization in visual acuity for 15 out of 25 macular degeneration patients, with a 5-year monitoring period [19]. Allen and Lowry reported an impressive set of results in treating several retinitis pigmentosa patients with a device that provided 200-μA peak bipolar current pulses (100 μA average) at ±9V and a single frequency (10 Hz), combined with nutritional supplements [20]. One young woman in the Allen-Lowry study had to give up her activities in the high school marching band. Retinitis pigmentosa had degraded her vision so much that she could not keep in step. In 1992, her visual acuity was $20/40^{-2}$ (right eye), 20/200 (left eye) and visual fields less than 15° before treatment. After electrotherapy treatment and nutrient supplementation, her vision improved to $20/20^{-}$ (right eye), $20/40^{+3}$(left eye), and her peripheral vision increased to 55°. As of 1998, she was self-administering therapy with a home unit and her vision stabilized. Keep in mind that, prior to seeking electrotherapy, all of these macular degeneration and retinitis pigmentosa patients were told by their ophthalmologists that there was no treatment for their visual disease.

Another study conducted by Allen, Jarding, and Zehner compared the use of nutrients only with the combination of nutritional supplementation and electrotherapy [21]. For the macular degeneration patients who were receiving nutritional treatment only, there was an average loss of three letters per eye on the Snellen chart over a 2-year period. During the same time period, the macular degeneration patients who received electrotherapy gained an average of 8.5 letters of visual acuity on the Snellen chart per eye.

One of the more complete series of electrotherapy studies for macular degeneration has been conducted by John Jarding, O.D., and Acuity Medical. In early 1991, when Dr. Leland D. Michael became terminally ill, he asked Dr. Jarding to continue his research in the application of electrotherapy and nutrition to macular degeneration [21]. The results Jarding has reported involve clinical studies and follow-up studies that have been ongoing since 1985. After completion of several phases of an IRB clinical study, Dr. Jarding successfully completed a series of FDA feasibility double-blind clinical trials.

Dr. Jarding's initial pilot studies used a number of commercially available electrotherapeutic devices. As the effort increased, concerns associated with device cost, reliability, performance consistency, operability, and clinical environment interface motivated Dr. Jarding to develop the TheraMac electrotherapeutic device that was designed specifically for visual disease problems such as macular degeneration, diabetic retinopathy, and retinitis pigmentosa. As of 2002, more than 6,500 treatments were given with no significant adverse effects. During one short-term study, 247 patients (average age of 76 years) received eight treatments during a 4-day period. By the end of treatment eight, the visual acuity of 246 of these patients increased 2.6 to 3.4 lines on the Snellen chart.

The data from an FDA double-blind clinical trial (Feasibility Phase), from a 34-patient study, and from a 404-patient IRB study are available. The results show that, depending upon the level of current used, 26% to 61% of the patients demonstrated visual acuity improvements of two lines or better on the Snellen chart after being treated with the electrotherapeutic device and protocol developed for TheraMac.

In 1998, Dr. John Jarding, myself, our wives, and Dr. Jarding's attorney formed a corporation to initiate an electrotherapeutic device development effort. This is what eventually became the company, Acuity Medical, and the electrotherapeutic device, TheraMac. I remained an officer of the company (which at that time was called BionErgy Therapeutics) until March 2000. Over the years, I have done consulting work for BionErgy and Acuity Medical as an electrical engineer, cell biologist, and business analyst. You, the reader, should know that I am a shareholder in Acuity Medical.

Our efforts produced a treatment protocol and two patents (J. B. Jarding and G. D. O'Clock, U.S. Patent Office # 6,035,236 and # 6,275,735, Methods

and Apparatus for Electrical Microcurrent Stimulation Therapy). During that time, Dr. Jarding was finishing his open label studies and was preparing to make the transition over to the FDA's more formal double-blind study environment. The initial electrotherapy study involving macular degeneration patients was handed over to Dr. Jarding by Dr. Leland Michael, who was terminally ill. Dr. Jarding knew that he was going to have to invest a lot of time and money into this effort if his goals involved being scientific, rigorous, complete, legal, and credible. He also knew that this was not going to be easy, and there would be no short cuts.

During the early phases of this effort, as Dr. Michael's illness progressed, his claims of clinical success were becoming an irritant to a number of ophthalmologists. They were becoming more and more concerned that Dr. Michael's success claims might be exaggerated. Most ophthalmologists routinely inform macular degeneration patients that there is no treatment for dry macular degeneration, and with time, visual acuity will only get worse. But the macular degeneration patients who were receiving nutritional supplementation and electrotherapy from Dr. Michael were noticing stabilization and improvement in their visual acuity. Impossible! This could not be true! As a result, Dr. Michael was threatened by ophthalmologists who were taking their complaints to State Optometry Board. They also threatened to take their charges and complaints to the State Attorney General's Office. This is the acrimonious environment that Dr. Jarding inherited when he agreed to continue the research that Dr. Michael initiated.

Not long after he took over, Dr. Jarding changed the protocol that Dr. Michael was using. Dr. Michael emphasized the nutritional aspect and used electrotherapy as an adjunct. Dr. Jarding turned this around and emphasized electrotherapy. Then, the unthinkable happened. Macular degeneration patients were beginning to respond much more dramatically. And some of the patients told their ophthalmologists that they did not want to follow any recommendations that were not approved by Dr. Jarding. It was upsetting enough that an optometrist was conducting a scientific study and providing a very safe and effective treatment for a visual disease that is supposed to be untreatable. But the real insult occurred when patients began to value recommendations from an optometrist over those given by ophthalmologists. Ophthalmology had had enough of this troublesome optometrist's invasion of their sacred turf. They attempted to use the power of the State Attorney General's office and the State Board to put Dr. Jarding out of business. Ophthalmologists voiced a number of concerns on the assumption that scientific protocol was not being followed, and Dr. Jarding's visual improvement claims had to be false. They tried to accuse Dr. Jarding of doing something illegal. Those who attacked Dr. Jarding had power, but no evidence. They tripped over their own assumptions and were not aware that Dr. Jarding was conducting his open label studies under FDA

supervision and FDA guidelines. He was following scientific protocols. Dr. Jarding's claims were valid and based on solid results. The attempts to shut John Jarding down failed.

There are some excellent ophthalmologists who have participated with various health care practitioners in a number of studies involving nutritional supplements and electrotherapy. And these particular ophthalmologists cooperate with, communicate with, and value the optometry profession. But ophthalmologists often have to endure severe criticism from their peers when they show this level of cooperation, intellectual curiosity, and concern for their patients.

There is more to this story, and there is one part in particular that will leave an impression on me for the rest of my life—and this kind of behavior is not limited to ophthalmology. After receiving treatment from Dr. Jarding, some of the patients returned to their ophthalmologists for an eye exam. The patients were delighted that the visual fog they had to look through was gone, and they could see color. Upon giving their ophthalmologists this information, the patients noticed that their eye exams were very "rushed." For a person with normal vision, the eye exam needs to be done carefully, and should not be rushed. A macular degeneration patient needs even more time, especially if their field of view is still limited. Some of them need to be allowed to trace the numbers on a color chart with their fingers. But those macular degeneration patients who were treated successfully by Dr. Jarding were being rushed in their ophthalmology eye exams.

For example, many macular degeneration patients recover some color vision after receiving electrotherapy. But they could not demonstrate this recovery during their ophthalmology eye exam. The color chart would be pulled away very fast before they could make a decision. Also, several of these patients said, "Just about the time I am ready to read the letters on the Snellen chart, my ophthalmologist changes the lens. He keeps flipping those lenses faster and faster. It was like, he didn't want me to show any improvement in visual acuity." The behavior of the ophthalmologists who tried to shut down both Dr. Michael and Dr. Jarding brings up some questions concerning ethics. When macular degeneration patients receive electrotherapy treatments and their visual acuity improvements allow them to take long walks and participate in outdoor activities, start to see color again, read newsprint again, reapply for their driver's licenses, and play golf again (well enough to register for golf tournaments, and find their own golf balls), and a particular group within the medical profession tries to stop this, we simply have to question their ethics.

8.4 Electrotherapy Clinical Studies: Cancer and Hemangioma

The clinical results for approximately 13,000 cancer patients treated with electrotherapy from the early 1980s to 2006 indicate that Nordenström's

NEAT-EChT technique is a relatively low-cost, safe, minimally traumatic, and effective cancer treatment option. The results achieved in China have been particularly impressive in the treatment of a wide range of malignant and nonmalignant tumors [22]. Electric currents in the range of 60 to 80 mA with voltages of 6V to 8V have been applied in the treatment protocol. The total charge applied (product of current and time) has been 80C to 100C per 1.0 cm of tumor diameter for malignant tumors and 30C to 40C per 1.0-cm diameter for certain types of hemangioma tumors. Five-year survival rates for stage I and stage II cancer patients treated with NEAT-EChT are 76.9% and 61.8%, respectively [22]. Five-year survival rates for hemangioma patients are in the range of 81.7% to 100% [23].

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review indicates that the 5-year relative survival rate for all cancer patients in the United States is approximately 62%. The U.S. statistics appear to be heavily weighted by a large percentage of stage I and stage II cancer patients, and they also appear to be influenced by a large percentage of cancer patients with tumor sizes significantly less than 5 cm [22]. The 5-year survival rate of Chinese cancer patients treated with NEAT-EChT is 69% for the combined stage I and stage II categories and 53% if the significant number of stage III patients, with very large tumor diameters, are included. As a bonus, as adjuncts to NEAT-EChT, low-dose chemotherapy or low-dose radiation therapy can provide additional 9% to 14% increases in clinical effectiveness and 5-year survival rates [22].

The NEAT-EChT results associated with treating middle and late stage lung tumors are impressive. NEAT-EChT survival rates for 1, 3, and 5 years were 85.6%, 56.3%, and 28.4%, respectively. The NEAT-EChT voltages applied were in the range of 6V to 8V with currents of 40 to 100 mA. Electric charge applied was 100 C/cm of tumor diameter. The therapeutic efficacy of the NEAT-EChT technique improved with lower currents (40 to 60 mA) and longer treatment times (2.0 to 2.5 hours) [24]. The results indicate that NEAT-EChT therapeutic effectiveness for middle and late stage lung tumors is second to surgery and better than radiation therapy or chemotherapy. Also, NEAT-EChT apparently does not develop a "resistance" that moderates or suppresses the effects of multiple treatments, as is the case for radiation therapy and chemotherapy [25].

The results of a NEAT-EChT clinical study by F. R. Douwes, M.D., and A. Szasz, Ph.D., at the Klinik St. Georg, Bad Aibling, Germany, were reported in the *1997 Proceedings of the Fourth International Symposium on Biologically Closed Electric Circuits* [26]. They wrote, "Electrochemical cancer destruction has its own pathology. The electric injury (due to the therapeutic technique) cannot be compared with injuries of other genesis. It is not burning: it is normally painless and not infected. The lesion should not be cut out or amputated.

The rejection of the electrically induced necrosis starts after a few weeks and leads to a smooth and indolent scar. Electroscars build no kelloids or secondary malignancies." The total charge per treatment that they reported was 30 to 80 C/cm^3 of tumor volume.

In the 1-year study by Douwes and Szasz, out of 97 patients treated by NEAT-EChT for various forms of cancer, complete remission in the treated area was achieved for 73.2% of the patients. Partial remission was achieved for 22.7% of the patients. All responses occurred within four weeks after treatment. Of the breast cancer patients treated, complete remission was achieved for 67.6% of the breast cancer patients and partial remission occurred for the remaining 32.4%. Only 4.1% of the 97 cancer patients showed little or no response.

8.5 Little Lies, Great Big Lies—And Then We Have Statistics

The abuse of statistics in clinical studies often borders on the unbelievable. And if using statistics to intentionally mislead were a crime, then the abuse of statistics by modern medicine would border on criminal. One of the most common statistical abuse tools employed in clinical studies, marketing, and manufacturing involves what I refer to as "substantial inflation of negligible numbers and insignificant number groups," or SINNING.

SINNING is a devious and dangerous game. The practice of SINNING goes something like this. Consider a certain group of cancer patients. Let us assume that 1.5% of these patients survive 5 years or more, after initial diagnosis. A new chemotherapeutic drug is developed, and 100 patients diagnosed with this particular kind of cancer are given the option to take the new drug. The drug produces a considerable number of harsh side effects. But, after 5 years from the date of initial diagnosis, 2.0% of the original 100 patients are still alive. The increase from 1.5% to a 2.0% 5-year survival is not very impressive, and not very significant. In fact, this difference in small numbers could be due to random fluctuations (often referred to as statistical noise) or artifacts associated with the methodology. Nevertheless, a large amount of money has been spent on the study, and the data has to be presented in a favorable way. Well, the very small 2.0% 5-year survival statistic is a whopping 33.3% improvement over the very small 1.5% 5-year survival statistic. So, the clinical study results will be presented in such a manner that your attention will be focused on the whopping 33.3% improvement. I may repeat this recommendation again. Try to get your hands on the raw data before taking any percentage increase statistics seriously.

"Cooking the numbers" is as popular in clinical studies as it was at Enron and World Com. Enron!! World Com!! Tell me please! How do you overlook

$7.15 BILLION of improperly reported earnings? Between the two companies; How do you lose over $260 BILLION in less than a year? That amounts to more than $8,200 lost per second! Even if you douse the money pile with gasoline, you can't burn the money that fast! What they did would appear to require a lot of misguided ingenuity combined with the large selection of alleged corrupt practices revealed in court and in several books. But, I digress. We shall now make the transition from accounting abuse, back to the abuse of statistical tools in medicine.

SINNING appears to be part of cancer drug statistics that are reported after patients who take a particular drug are compared with patients who take a placebo. A number of newspaper articles reported results indicating that a very popular drug cuts a woman's breast cancer risk by 50%. Apparently, a number of alternative medicine practitioners looked at the raw data and clarified the meaning of the 50% increase. In the cohort that took the drug, less than 2% eventually were stricken with breast cancer. Of the cohort that took the placebo, less than 3% were stricken with breast cancer. First of all, what do the words "less than" imply for each of those numbers? Second, this again is inflating small insignificant numbers. But, some would say that 3% is a 50% improvement over 2%. Yes, but that so-called improvement may be just due to random fluctuations in data acquisition and methodology, clinical artifacts, bias, and so on, in an analytical approach that is known for its flaws.

A similar game is played in the graphical interpretation of clinical data. One of my favorite examples involves the use of logarithmic scales. This allows the investigator to make small variations look very significant, even when they are close to much larger variations. This is the graphical version of SINNING. A short article that appeared in the January 10, 2003 issue of *Science* provides a good example [27]. In this case, the Center for Disease Control (CDC) wanted to show that the introduction of the ring vaccination technique, utilized in West and Central Africa, had a much more dramatic effect than the data indicated on a linear graph. The linear graph clearly indicated that there was not much difference between the vaccinated individuals and the percent unvaccinated as far as the effect on number of smallpox cases reported over a 15-month period. But by using a logarithmic graph, the differences in higher smallpox numbers (from 200 to 1,000) could be compressed and the differences in smaller smallpox numbers (from 50 to 200) could be enhanced. The logarithmic decrease in the percent unvaccinated numbers involved only a factor of 2 decrease (80% to 40%), so the unvaccinated data did not decrease as much on the logarithmic chart as the smallpox case numbers. As a result, the very small reduction for smallpox cases looked very large in comparison to the change in unvaccinated. It appears that this is an example of "cooking the graph."

Then, there is the world of hypothesis testing, standard deviations, P-values, confidence intervals, t-tests, and so on, which is a neat collection of

statistical tools and parameters that have the power to impress, persuade, obfuscate, cloak, and boggle the mind.

These are useful tools for certain applications in a wide variety of fields including clinical studies, pharmacology, engineering, marketing, astronomy, and manufacturing. But these statistical tools are a bit complicated, often difficult to understand, and easy to manipulate. Let us look at an example that, although a bit oversimplified, illustrates how hypothesis testing and confidence intervals can be manipulated. In the following scenario, I am using a format that is similar to several examples that can be found in the book *Engineering Statistics* [17].

A group of 20 patients, all afflicted with a specific disease, has the opportunity to receive a new kind of therapy. A substance in the blood stream will be measured and used as the indicator of therapeutic efficacy. The normal level of this substance in the blood stream is 20 mg/dl, and this is the standard for a healthy individual. As a standard for therapeutic efficacy, the entire patient population must show an average of 20 mg/dl of this substance in their blood samples after therapy. An acceptable standard deviation of 2.4 mg/dl is specified. After the therapy has been administered to the 20 patient population, the results show that an average of 19 mg/dl is achieved by the small group of 20 patients.

Based on the data taken for this small sample of a much larger patient population, we might make the following hypothesis. The average level of 20 mg/dl is achieved for the entire patient population, if the entire patient population receives this treatment. The agency monitoring the clinical study wants to be sure that the probability of a low value error, associated with rejecting this hypothesis, is no more than 2.5% (0.025). A high value error of no more than 2.5% (0.025) is also specified. In this case, the error probability value (α, the probability of rejecting the hypothesis when it is actually true) is the sum of the two, or 0.05. This produces a normalized z-parameter value of ± 1.96. Therefore, the calculated values of magnitude for the z-parameter associated with our data (z_O) should be less than 1.96. If this is true, we can accept the hypothesis that the average level in blood for this substance will be 20 mg/dl if the entire patient population receives this particular therapy. Now, we can calculate the distance from the mean z-value to the lowest acceptable value for the level of the substance in blood:

$$\begin{aligned} z_O &= (\text{mean value} - 20)/(\text{standard deviation})/(\#\ \text{patients})^{1/2} \\ &= (19 - 20)/(2.4)/(20)^{1/2} = -1.863 \end{aligned} \tag{8.1}$$

Since the magnitude of z_O is less than 1.96, the hypothesis is accepted. The data provides results that are within the acceptable range of values, and above the lower limit.

At another clinical test site, 25 patients are given the same therapy for the same disease, and their average is also 19 mg/dl after therapy. But, according to (8.1), the magnitude of z_O for the 25-patient group is 2.083. This value is higher than the 1.96 limit. Therefore, the hypothesis has to be rejected for the 25-patient group. But why? The 25-patient group's average is the same as the 20-patient group's average, and both averages are very close to the 20-mg/dl standard.

From the above example, it is clear that the decision to accept the hypothesis or reject the hypothesis can be based on very small variations in statistical parameters and statistical specifications. This is an indicator of the difference between clinical significance (based on practical importance of data) and statistical significance (based on statistical parameters and rules). Clearly, both sets of results are clinically significant. The small differences in z-values are not meaningful for the patients who have achieved significant improvement in their blood chemistry and the health care practitioners who must objectively evaluate the therapeutic efficacy of the technique. And yet, in many important studies of therapeutic effectiveness, statistical significance dictates the determination of success or failure.

We might increase the confidence interval and specify a lower α value of 0.0102. This would give a z-value of 2.57 and we would now be well within the specified z-value limits for both groups, with a higher value of confidence. But all we are doing here is playing a game with variability and the acceptable range of values. This now allows more variability in the data between different groups of patients and different patient numbers. Massaging the data in this manner changes the statistical implications, but this kind of statistical juggling does not change the clinical implications for effectiveness, at least, not for a rational person.

From this example, it is fairly easy to see that statistical acceptance can depend upon slight manipulations of statistical parameters and specifications. And the statistical parameters and specifications required can be influenced or determined by a desire on the part of the evaluator to accept the results, or not to accept the results.

8.6 Double-Blind Clinical Trials: Gold Standard, Fools' Gold, or Gold's Fool?

The randomized double-blind clinical study has its roots in the results reported in 1937 by Gold et al. in the *New England Journal of Medicine*. A 1950 paper published by Greiner et al. in the *American Journal of Medicine* was one of the first to use the term "double-blind." After a clinical pharmacology review lecture on the double-blind technique was given by Gaddum in 1954, the use of this

procedure became quite popular in the medical community [28, 29]. In a double-blind environment, some patients are given the real treatment, and some are given the sham treatment (fake), which is often inappropriately designated as the "placebo." The choice of who gets the real treatment and who gets the fake treatment is random. Both those who administer treatment and the patients being treated are not aware of which treatment they are giving or receiving.

The double-blind approach can be referred to as the "Gold standard" simply because the idea was formally initiated by Gold. It is an idea that looks good on paper. But is the double-blind approach, with its associated statistical tools, really just fools' gold or maybe Gold's fool? The evidence of any scientific validity for the superiority of this technique is weak or nonexistent.

Randomized double-blind techniques have been considered as being superior to observational techniques (with controls) because conventional wisdom states that the observational technique consistently overestimates or exaggerates therapeutic effects. In the June 22, 2000, issue of the *New England Journal of Medicine*, Pocock and Elbourne vigorously defend the use of randomized techniques for clinical trials (such as the double-blind approach) because they believe that the randomized trials are not contaminated with personal choices and beliefs that can occur with observational studies [30]. Apparently, this opinion has very little basis in fact and very little scientific credibility. In fact, the hypothesis-testing example strongly indicates the same kind of data and results contamination can be introduced with the statistical tools utilized in double-blind studies. Personal choices and beliefs can be inserted much more easily and stealthy, and they can be cloaked or obscured under the complexity of the randomized double-blind statistical tools utilized. A double-blind study can be rigged by way of its statistical tools [29].

In the same issue of the *New England Journal of Medicine*, Benson and Hartz found little evidence that estimates of therapeutic effects in observational studies are either consistently larger or quantitatively different than the results obtained in randomized clinical trials [31]. Again, in the same issue of the *New England Journal of Medicine*, Concato, Shah, and Horowitz show evidence that the magnitude of treatment effects are not systematically overstated or overestimated in observational studies when compared with the same kind of therapeutic modalities and results using randomized controlled trials [32].

However, the most important consideration in the evaluation of the randomized double-blind clinical trial involves a topic that has been debated for more than 30 years. No matter how one tries to package it, in many situations the randomized double-blind clinical trial violates the Hippocratic oath, the physician's responsibilities to the patient, and the Declaration of Helsinki. In other words, the randomized double-blind clinical trial violates ethical principles [33, 34]. The fact that the randomized double-blind clinical trial is often unethical (sometimes to an extreme) has been no secret to medical practitioners [29].

A review of the medical literature shows that there is significant disagreement between medical doctors in the belief that the double-blind approach is any better than an observational study with good controls. They also disagree significantly on the definition and significance of the placebo effect, the proper use of the statistical tools, and the ethics of the double-blind approach.

A literature search from the period extending from 1937 to the present does not provide one paper that gives conclusive evidence that the double-blind study technique is more accurate than observational studies with controls. Considering papers that support the randomized double-blind approach, arguments that favor the technique appear to be rather qualitative and subjective. In addition, the validity of the statistical tools utilized in double-blind clinical trials has not been completely verified in the literature. Also, in my own statistical data acquisition and analysis efforts, I have come to realize a statistical fact that is often ignored. It is obvious in many instances that statistical results obtained from a sample of the population are often not consistent and not representative of the entire population. The validity and applicability of many statistical tools are questionable and limited because many of them depend upon an assumed close agreement between the results for a population, and the results for various samples of the population. The randomized double-blind clinical study technique appears to have been accepted by decree, without any serious attempt to verify its reliability or scientific merit [29].

The randomized double-blind clinical trial has a number of shortcomings: (1) it distorts the doctor-patient relationship; (2) statistical samples are often not a true representation of the population [35]; (3) the technique is highly sensitive to clinical artifacts; and (4) clinical significance is not the same as statistical significance [33]. From a true scientific standpoint, the randomized double-blind approach can never be considered a scientific or worthy standard until (1) the technique is rigorously proven to be significantly more accurate than observational approaches (with good controls), (2) better evidence is presented that establishes the validity and applicability of the statistical tools utilized, (3) better controls are established for statistical parameters that are either quite variable or highly nonlinear, and lead to different conclusions with slight adjustments in parameters, (4) the technique incorporates more transparency, (5) reliability is improved for certain statistical parameters (i.e., P-values; see [36]), and (6) guarantees are provided that the technique does not have serious problems with ethical compromise. And that is just the beginning.

I never take the results or conclusions from a double-blind clinical trial seriously unless I can see the raw data, or unless I see an accompanying observational study, with controls. The randomized double-blind clinical study offers too many opportunities to manipulate or rig the study (providing conclusions that the promoters or detractors want to hear), mask or cover up valid results, and reach significantly different conclusions with small changes in parameters or

technique. Some refer to the randomized double-blind study approach as medical voodoo. In many applications, that appears to be true. It appears to be useful in some areas. But as far as I am concerned, the randomized double-blind technique offers no improvements in accuracy compared with the observational approach, it is much more complicated and it is often unethical. In fact, one of the elephants in the room of randomized double-blind studies involves the unethical nature of the technique [37–42]. The only weapons the medical community has that enable clinical researchers to ignore this particular defect are denial and self-deception.

8.7 Summary

The clinical studies for the electrotherapeutic treatment of wounds, visual disease, and cancer indicate that patient response to electrotherapy is very high from the standpoints of healing, visual acuity improvement, and tumor remission. Just viewing electrotherapy results and comparing them with other therapeutic techniques clearly validates the therapeutic efficacy of electrotherapy as it is applied to a variety of health problems and disease. There is no question concerning the clinical significance of electrotherapy. It has over 140 years of reported research results and success behind it. Electrotherapy also has roots that go back more than 2,000 years.

As effective and miraculous as electrotherapy can be, the results can be masked, cloaked, and suppressed by a variety of statistical tools and clinical study techniques that are often designed or manipulated to protect the status quo.

Sometimes the efficacy of electrotherapy is simply too good, too obvious, and too consistent to be masked and suppressed even by the most convoluted statistical techniques and clinical study protocols. So what then? How can high-quality electrotherapy results be suppressed and blocked out of the medical mainstream? The method is simple, and it has been imposed upon NEAT-EChT. In order to keep NEAT-EChT out of the medical mainstream, all that one needs to do is restrict its clinical application to a patient population that does not have long to live. In two attempts to study the effects of NEAT-EChT in the United States, the only cancer patients that were allowed to be treated were those who have exhausted all other conventional approaches to cancer therapy (i.e., radiation therapy, chemotherapy, and surgery).

In most cases, by the time a cancer patient has gone through all three of the conventional cancer therapy approaches, their GI tract has been permanently damaged (along with other organs), their immune system has been severely compromised (or destroyed), and vital organs and tissue have been removed. Most of these patients have less than a few months to live. Positive

initial results were achieved, but that is all you get with this group—initial results. There is no possibility for follow-up to evaluate long-term prospects, and no possibility to evaluate rate of tumor regression or remission. These cancer patients have died before this work can be completed. To add insult to injury, some medical practitioners will imply that the electrotherapeutic technique contributed to the death of a cancer patient whose health was severely compromised by radiation, highly poisonous chemotherapeutic agents, and surgery.

It appears that NEAT-EChT, an electrotherapeutic technique that has prolonged and saved many lives, has been willfully restrained and blocked from the medical mainstream in the United States. This is one of the many electrotherapeutic techniques that offer safe, reliable, patient-friendly, low-cost, complementary and therapeutically effective treatment choices for a wide range of health problems.

Heaven knows, the medical community needs therapeutic and diagnostic procedures that offer advantages in safety, therapeutic efficacy, reliability, and cost. Please read this Summary again. Then, as an exercise, read reference [50] of Chapter 1 if you have not done so already. After reading that particular article, you will realize that I am not just some wild man out on the Minnesota prairie, picking on the medical profession and being overly critical. After reading reference [50] of Chapter 1, ask yourself the following questions: What is a medical doctor's greatest fear? What profession is becoming medicine's most severe critic? Then ask yourself: What can we do to help?

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9

Recent Developments and Trends

9.1 Introduction

The February 8, 2002, issue of *Science* has some very interesting papers in a special section on "The Bionic Human." Some of the artificial body parts, materials, and substances discussed included fully functioning artificial limbs, mechanical hearts, myelin sheath repair, artificial blood (hemoglobin based and perfluorocarbon based), artificial liver (a special kind of bioreactor), retinal implants (integrated circuits), tissue engineering (from human and animal sources), and bioactive polymers.

An article in the June 2006 issue of *Scientific American* discusses the development of a technology and manufacturing methodology to build sophisticated biological devices using biofabrication techniques that are based on some the methods utilized in modern semiconductor material/device fabrication systems [1]. The authors discuss the possibility of building genetic circuits by manufacturing long segments of DNA. A paper published in the October 2005 issue of the *Proceedings of the IEEE* provides some thoughts on integrating nanoscale semiconductor devices with biological materials and biological structures. This technology can provide the capability to control biomolecular processes and interactions, and control and modify the structure, function, and properties of biological systems [2]. There is definitely a bright side and a dark side to all of this.

A virus-based scaffold has been evaluated for the synthesis of semiconducting nanowires [3]. And the fabrication of three-dimensional interconnect arrays has been reported [4]. High-aspect-ratio submicrometer silicon needles have been fabricated that can interface with living cells [5]. Some might disagree with this statement, but developing fabrication techniques for interconnects and

interfaces between devices is often more difficult than developing the devices themselves. In fact, one of the more critical locations for potential interference (electromagnetic, chemical, mechanical) is the area where electrodes make contact with tissue [6]. Once the interconnect and interface problems are solved, it is only a matter of time before the technology becomes a reality and matures.

When all of this happens (not if, but when), therapies involving exogenous stimulants will not disappear. However, our capabilities to become similar to and interact with natural biological systems will be significantly enhanced. And some of these new integrated nano-bio elements might cause more problems than they solve. For instance, the possibility of injecting self-replicating nano-bots into our cardiovascular and lymphatic systems—for various immunological, custodial, and repair functions—has been discussed for some time. A "hunt and kill" nano-bot has been proposed that seeks out pathogens and zaps them with an on-board microlaser.

So, what happens if these little guys acquire something like an autoimmune response and they start zapping our own tissues and our own friendly red and white blood cells? Also, one might be a bit concerned about these self-replicating bots replicating out of control (like viruses). Can these nano-bots aggregate, just as colloidal particles and cells will do under specific conditions, producing an effect like an atherosclerosis or thrombosis? But we might think, "No problem! That technology and those possibilities are far in the future." If that is what we believe, we are wrong. All of this will probably become a reality in my life-time (and I'm old).

The future is already here. In fact, it arrived yesterday.

9.2 The Growing Interrelationship Between Electro-Assist Devices and Electrotherapeutic Devices

We often think of cardiac pacemakers and defibrillators and certain implant devices for neurological disease and artificial vision as electro-assist devices. However, the dividing line between the world of electro-assist and electrotherapy is becoming somewhat blurred. Electronic implants for deep-brain stimulation have been useful in treating victims of stroke, Parkinson's disease, and other neurological disorders including depression [7–9]. Many of these implanted electrical stimulation devices provide a near-term "fix" for the health problem. But in some cases, their long-term use could promote a therapeutic effect that would help to mitigate the health problem.

One example of this involves the area of artificial vision. In the mid- to late 1960s, Brindley and Lewin reported the results of an artificial vision electrode system connected directly to the visual cortex of a blind patient [10]. They were able to induce phosphene responses. Weiland and Humayun have written a

paper on retinal implants that would be applicable to those suffering from age-related macular degeneration (AMD) and retinitis pigmentosa [11]. They indicate that threshold of detection requirements for retinal component stimulation is in the range of 50 to 100 nC for minimal contrast detection and safety (to keep from damaging retinal tissue and damaging the very small diameter electrodes). They propose using approximately 2,400 iridium oxide electrodes (65 to 100 μm in diameter) stimulating the 5-mm diameter macula. If each electrode is capable of supporting 100 nC, the total charge would be 240 μC. The 0.2-cm^2 area of the macula would be stimulated with approximately 1.2 mC/cm^2. From the standpoints of potential retinal tissue damage, potential neural damage, and formation of potentially harmful reactants (such as H_2 or O_2 gas), the 1.2 mC/cm^2 charge density is well within the combined effective and safe range of 0.8 to 4.8 mC/cm^2 as reported by the authors. A charge of 240 μC from an artificial vision device within the area of the macula would amount to 2 μA for a total time duration of 2 minutes in that region. In comparison, an electrotherapeutic current of 120 μA into the retinal area produces a current density of approximately 0.017 mA/cm^2. The electrotherapeutic current in the 0.2-cm^2 area of the macula would be approximately 3 μA. This current level indicates that the current delivery capabilities of some retinal implant devices may be capable of serving as both a visual assist device and an electrotherapeutic device. To date, some of the retinal implant devices seem to exhibit this capability and others do not. The ability to serve as a visual assist device and electrotherapeutic device may depend upon a variety of factors including location of the retinal implant, size of electrode, level of stimulation, and duration of stimulation.

My mind often boggles when I look at the incredible improvements in materials, devices, and systems that have occurred over the past 15 years for electrical, magnetic, and electromagnetic techniques that provide assistance and therapy for a variety of health problems including cancer, visual disease, and neurological disease. But as incredibly advanced as this technology base seems to be, we appear to be terribly medieval in our thinking with respect to applications. We are blasting people with 1T to 2T magnetic fields to treat depression and certain neurological disorders, when magnetic fields that are one hundred billion times less intense will often be just as effective and consistent. We have noninvasive electrotherapeutic and magnetotherapeutic techniques to treat depression, stroke, Parkinson's disease, and pain. But an electrotherapeutic approach that is often favored involves very invasive deep brain stimulation.

Medicine has also been slow to reintroduce electrotherapy for the prevention, mitigation, and control of visual disease. Noninvasive techniques are available that help a person with visual disease to maintain visual acuity and quality at a relatively low cost. But many medical professionals tend to ignore the easy, patient-friendly, and low-cost approaches. They tend to get more excited about

the prospects of expensive microchip retinal implants that allow a patient to see only phosphenes and blurry shadows.

Some medical professionals reject the noninvasive electrotherapeutic approach and prefer to stick an electrode deep inside someone's brain to treat depression. Our medical approach seems to be immersed in a culture of extremes. If we are sick, they blast us with chemo, radiation, gene therapy, 2T magnetic fields, deep brain stimulation, and retinal implants. And the reason is probably not just medieval thinking. Could the motivation for therapeutic and diagnostic extremes involve the relatively high levels of revenue and control that these options offer? What is your opinion?

9.3 Projections

As of the publication date of this book, most of the electrotherapy devices and sources are, essentially, simple or complex signal generators. The first generation of these devices involved simple devices and probes that delivered a direct current. The second generation provided electrical stimulation with a limited range or limited choice of individual frequencies that were manually selected. The third generation concentrated on delivering specific waveforms with a wider range or selection of frequencies. The fourth generation electrotherapeutic device provides automatic frequency control and more sophisticated monitoring. The implantable devices with applications in oncology, neurological disorders, and visual disease will be in the family of fifth generation electrotherapeutic devices. They will pave the way for the increasingly miniaturized, bio-fabricated and biocompatible devices that will be highly integrated with the tissues and organs of the body. As time goes on, it may become more and more difficult to distinguish between the artificial implant and the original tissues and organs of the body.

The large numbers of biomaterial and biosystem assist and prosthetic devices that are anticipated will suffer some of the same problems that occur when many functions are integrated into electronic systems. That problem will involve interference. Since many of these biomaterials and biosystems will be electrotherapeutic or magnetotherapeutic, they will be susceptible to EMI. One example that is currently of concern involves the interference between electrotherapeutic devices and cardiac assist devices (pacemakers, defibrillators, and so on). For future applications involving nanotechnology, the trajectory of a nano-bot could be significantly altered by external magnetic fields. The interference problem is not limited to EMI. The interference problem can sometimes be more associated with biomechanics. For instance, swinging the arm that is closest to an implanted pacemaker can result in an increase in pacing rate [12]. Having a conversation during exercise can also reduce the pacing rate [13].

With respect to clinical engineering, one of the interesting areas of Dyro's *Clinical Engineering Handbook* [14] involves the enhancement of engineering services in the clinical environment. With the massive influx of technology and new techniques, the presence of only medical doctors and nurses in the operating room will no longer be adequate or safe. The scope of engineering services will eventually include engineers in the operating room and in preoperative and postoperative care. A few years ago, there were a number of articles in news magazines that revealed the questionable participation of a sales person showing surgeons how to operate a new surgical device. Yes, you read that correctly. The sales person actually participated in the operation. The reason for this was simply that the surgical device and technique required new knowledge, new attitudes, and new skills that the surgeon did not have at that moment. The surgeon was frustrated and very upset. The procedure was not going well. Nothing worked right. Obviously, there was very little pre-op planning and not much "thinking ahead." The sales person had the knowledge, attitude and skills to follow through. Apparently, he also had an appreciation for the art involved in this kind of surgery. After reading this, I wondered, "Who would I want to operate on me? Would I prefer a frustrated and angry surgeon (with shaking hands), or a sales person who knows the technology and knows how to use the surgical tools?" Insert the words "clinical engineer" for the word "salesperson" and you might have a little preview of part of biomedical engineering's future. From a near-term standpoint, I believe that engineering services will become more involved in preoperative and postoperative care (especially with implants). As time goes on, I believe engineers will become more intimately involved in the surgical process. We have the precursor to this right now in the operating room. There are medical professionals in the operating room who have M.D.-Ph.D. degrees. And some of those Ph.D. degrees are in engineering.

With respect to the introduction of the more noninvasive and less expensive electrotherapeutic and magnetotherapeutic techniques in U.S. hospitals and clinics, I believe this will be a long slow process. But it will happen. For example, some hospitals and clinics now provide access to chiropractic, acupressure, and acupuncture care for patients. They do this simply because, for some health problems, those techniques often work much better than the allopathic drug–surgery alternative. But it took a long time for this kind of integrated approach to happen. One of the reasons why chiropractic care and acupressure became more acceptable is because those are the kinds of treatments many retired medical doctors eventually chose for their own health needs involving severe back pain, shoulder problems, and headaches.

Noninvasive or minimally invasive electrotherapeutic and magnetotherapeutic techniques are available in many places outside the United States including Australia, China, Europe (including Germany and Greece), Korea, and Latin America. As more and more patients from the United States become

aware of the success rates and relatively low costs that are available with electrotherapy and magnetotherapy in other countries, many of them will decide to get treatment outside the United States. This will have an effect on revenue and control for U.S. medicine. When a substantial amount of revenue and control have been lost, there will be an adjustment in the attitudes, policies, and procedures of the medical community.

One of the positive impacts that implanted electrotherapeutic and magnetotherapeutic devices will provide along with the oncoming biomolecular and nanotechnology devices will be that modern medicine will be forced to recognize the *Body Electric*. Any attempt to confine the new approaches toward assistance, prosthetics, and therapy with only chemistry and anatomy will prove to be inadequate. Physics will become as important as chemistry and anatomy in the training of future medical professionals. Cell biology will be forced to clean house. The Body Electric will have to have the same importance and attention in medical education as is given to gross anatomy. And when medical educators do this, ethics and decency will require them to remember people like Galvani, Aldini, Matteucchi, du Bois Reymond, Szent-Györgyi, Becker, Nordenström, Ling, and many others who provided the results that brought them to this place. Medicine must remember and give credit to the people who gave the knowledge that medical professionals desperately need so that they can become better healers rather than being a major source of the disturbing groups of health problems that are categorized under the heading of iatrogenic disease.

9.4 Summary

Certain elements of sophisticated biological devices, using biofabrication techniques similar to those associated with modern semiconductor material/device fabrication, are being developed and tested. Available technology is now capable of building moving parts and chemically active elements that are smaller than certain components of a cell. Nanotechnology is providing the capability to fabricate subsystems at the molecular level. These technologies can provide enhanced capabilities and performance levels for many electro-assist and electrotherapeutic devices.

One of the positive impacts that implanted electrotherapeutic and magnetotherapeutic devices will provide along with the oncoming biomolecular and nanotechnology devices will be that modern medicine will be forced to recognize the Body Electric.

In addition, the dividing line between the world of electro-assist and electrotherapy is becoming somewhat blurred. In some cases, and electro-assist device (such as an artificial retina) could also provide a therapeutic benefit.

The rigors and demands of new technologies and techniques will eventually require biomedical engineers and clinical engineering services to actively participate in preoperative, operative, and postoperative procedures.

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Appendix
Answers to Chapter Exercises

Chapter 1

1. (a)

Iatrogenic Problem	Deaths Per Year	References
Adverse drug reactions	100,000	[1]
Medical error	195,000	[2, 3]
Nosocomial infection	26,000 to 80,000	[4, 5]
Malnutrition	108,000	[6, 7]
Outpatient care	199,000	[5]
Unnecessary procedures	12,000+	[5]
Surgery	?	?
Bed sores (pressure ulcers)	115,000	[8]
Total annual deaths due to iatrogenic disease	755,000+	

Medical professionals will often point to the approximately 20 million hospital admissions per year and insist that the 755,000 iatrogenic deaths represent *only* 3.8% of the admissions and that their resulting 96.2% success percentage is quite good. Not so fast! Many patients survive in spite of their health care, and not because of it. Also, many of the admissions are multiple admissions.

In some cases, the multiple admission is due to a previous medical mistake and the patient eventually dies during the time period of the last admission. So, a 96.2% patient survival does not necessarily reflect on the quality of medical care as much as it reflects upon the capabilities that patients have in order to survive multiple traumatic events and mistakes in a health care environment. Also, iatrogenic events contribute to other patient disasters. Drug-induced ulcers and drug-induced Parkinson's disease have become major disasters for more than 100,000 patients per year. So, in some cases, the patient does not die. But the iatrogenic event simply adds the burden of another disease—sometimes more terrible than the one they already have.

(b) You will find that the number of alternative medicine–related deaths per year is very low (fewer than 300) compared with the hundreds of thousands of deaths attributed to iatrogenic disease.

(c) (755,000 Annual Iatrogenic Deaths/2)/10,000 Hospitals = 37.75 Iatrogenic Deaths per year per hospital.

(755,000 Annual Iatrogenic Deaths/2)/40,000 Clinics = 9.43 Iatrogenic Deaths per year per clinic.

Based on averages, these death statistics per hospital and per clinic appear to be reasonable, and might possibly be understated.

Before we point too many fingers at hospitals, clinics, and medical doctors, there is another aspect that we might need to consider. In the May 9, 2006 issue of the *Minneapolis Star Tribune*, a very interesting article by Paul Krugman of the *New York Times* states that "being American seems to damage your heath regardless of your race and social class" [9]. The title of Krugman's article is "Americans of All Stripes Are Sicker Than They Need to Be." Krugman outlines the some of the problems that the medical profession in the United States has to face with respect to its patient population. He cites a 2006 study in the *Journal of the American Medical Association* that shows Americans are much sicker than the English (who are not all that healthy themselves). "Middle-age Americans are twice as likely to suffer from diabetes as their English counterparts." American health is so poor that the "richest third of the American population is in worse health than the poorest third of the English." Factors that appear to affect poor American health are the tendency towards obesity in America, insurance companies that are unwilling to pay for preventative measures but are willing to pay for extreme measures (like amputations, bypass surgery, and chemotherapy when people fail to follow preventative measures), and stress due to our workaholic economy. It does appear that there are a number of things associated with American attitudes and

ways of life (or behavior risk factors) that are seriously bad for our health. And this is the condition that U.S. medical care has to face in dealing with a significant portion of the American patient population.

(d) The National Decubitus Foundation indicates that costs associated with bedsores are $55 billion annually. Costs of other iatrogenic problems appear to add another $32 billion to $109 billion to the costs. At this point in time, U.S. health care costs are in excess of $2 trillion annually, and impose a 15.3% burden on the Gross National Product. An article by S. Lee and D. Roth indicated that, by using economic acceleration and amplification factors, the federal government valued each life year at $600,000 [10]. If that number can be believed, the loss of life due to iatrogenic disease has an economic impact on productivity and consumption of approximately $453 billion per year. If that number is not believable, and if the income and purchasing power of these individuals is coupled with a few economic acceleration coefficients, the annual productivity of each individual might be set at $52,000. Multiply $52,000 per year by the 755,000 annual deaths due to iatrogenic events and we have a productivity economic impact of approximately $39 billion per year. So, one could say that the costs of iatrogenic related events in the United States are somewhere between $39 billion and $453 billion per year.

2. (a) With no other information, we might assume a proportionality relationship involving the power absorbed and dissipated by the tumor (P_{TUMOR}) and the power dissipated by the body (P_{BODY}) as having the same ratio as the 2-cm-diameter tumor area (A_{TUMOR}), and the body area (A_{BODY}):

$$(P_{TUMOR})/(P_{BODY}) = (A_{TUMOR})/(A_{BODY})$$
$$= 3.14 \times 10^{-4}\ \text{m}^2 / 1.8\ \text{m}^2 = 1.74 \times 10^{-4}$$

$$P_{TUMOR} \approx \left(1.74 \times 10^{-4}\right)(100\,\text{W}) = 0.0174\,\text{W} \approx I_{DC} V_{DC} = I_{DC}(8\,\text{V})$$

$$I_{DC} \approx 0.0174\,\text{W}/8\,\text{V} = \underline{2.18\ \text{mA}}$$

(b) $R_{TUMOR} = V_{DC} / I_{DC} = 8\text{V} / 2.18\ \text{mA} = \underline{3{,}669.7\Omega}$ (which is in close agreement with a number of research papers concerning impedances associated with normal and malignant tissue samples that are dry).

(c) The area of the outer periphery of the 2-cm-diameter and 1-cm-deep tumor is 3.14 cm^2. J (current density) = I/A = 2.18 mA/ 3.1414 $\text{cm}^2 \approx \underline{0.7\ \text{mA/cm}^2}$.

This value is very close the current densities associated with a number of electrotherapeutic applications that will be discussed in other chapters.

3. The tumor mass is not just tissue, but it consists of a tumor tissue-vascular-fluid matrix combination (in a parallel circuit configuration) where most of the current is flowing through the fluid matrix and vascular structure associated with the tumor. In this case, the 8V applied voltage produces and total current of 58.9 mA, but only 2 mA of that total current is actually flowing through the tumor tissue. Tumor tissue impedance varies with time, but it can be in the range of 2,500Ω to 5,000Ω. So the calculation in Exercise 2(a) is fairly close to t he actual tumor tissue current value. Estimates reveal that approximately 1.5% to 4% of the total current being supplied to the tumor tissue mass actually flows through the tumor tissue. Most of the current being supplied to the tumor mass flows through the liquid matrix and the tumor vascular structure.
4. (a) $(P_{TUMOR})/(P_{LUNG}) = (A_{TUMOR})/(A_{LUNG}) = 3.14 \times 10^{-4}\ m^2 / 0.08\ m^2 = 39.25 \times 10^{-4}$.

   $P_{TUMOR} \approx (39.25 \times 10^{-4})\ (5W) = \underline{0.0196W} \approx I_{DC}\ V_{DC} = I_{DC}\ (8V)$

   $I_{DC} \approx 0.0196W / 8V = \underline{2.45\ mA}$

   (b) $R_{TUMOR} = V_{DC} / I_{DC} = 8V / 2.45\ mA = \underline{3{,}265\Omega}$
5. (a) Area on one side of the cell = $4 \times 10^{-6}\ cm^2$. Current density X Area = $(1\ mA/cm^2)\ (4 \times 10^{-6}\ cm^2) = 0.004\ \mu A$. Power per cell (both sides of cell) = 2 (membrane voltage)(current) = $2(0.07V)(0.004\ \mu A) = \underline{0.056 \times 10^{-8}\ W/cell}$. I may be right, or I may be wrong, but I approached this problem assuming that the current appears to be transversing the membrane structure on two sides of the cell. Therefore, two membrane regions are involved and two 70-mV membrane voltages are associated with the current. This highly oversimplified model is not complete or consistent when the current is split up into different dedicated ion channel pathways, or when other cell models are considered. However, for simplicity and for now, we will treat a cell membrane as a 17.5-MΩ resistance to ionic current. The product of the current and the resistance yields the 70-mV plasma membrane voltage. The product of the voltage and current, or the current squared and the membrane resistance for one membrane side is 0.028×10^{-8} W/cell or 0.056×10^{-8} W/cell for both membranes. This oversimplified model will be addressed again in Chapter 7.

   (b) *Power* (for human body) = $(5 \times 10^{12}$ cells) (0.045) $(0.056 \times 10^{-8}$ W/cell) = $\underline{126W}$. Yes, this value of power for the human body is very

close to the 100W value provided in Exercise 2. Should we include some *native and foreign cells* in this calculation, and in the material addressed in the following chapters?

6. *Power* = (4,186 J/Cal) (0.029 Cal/sec) = 121.4 J/sec = 121.4W.

7. (a) If high cellular activity produces average current densities of 1 mA/cm^2, one could assume that, for applications other than visual disease and direct contact with nerve tissue, therapeutic current densities up to this level should be therapeutically efficacious and reasonably safe (1 $mA/cm^2 = 1{,}000\ \mu A/cm^2$).

   (b) *Power Density* = (membrane voltage) (current density) = (70 mV) (1 mA/cm^2) = 70 $\mu W/cm^2 \approx V_{APPLIED}\ I_{APPLIED}/Area = (8V)\ I_{APPLIED}$ / (7 cm^2) = (1.143 V/cm^2) $I_{APPLIED}$. Therefore, $I_{APPLIED} \approx (70\ \mu W/cm^2)$ / (1.143 V/cm^2) = 61.2 μA. Yes, according to the information given, this current level is reasonable, and safe.

   (c) *Source Voltage* = (current)(resistance) = [(1 mA/cm^2)(3.1 cm^2)] (1,000Ω) = 3.1V (This source voltage seems a bit low.)

   Treatment current = (1 mA/cm^2)(3.1 cm^2) = 3.1 mA. (This would be a *reasonable current level for certain wound healing applications*, but not for visual disease applications.)

8. Assuming that *radiation* is the only heat transfer mechanism available, according to the Stefan-Boltzmann relationship: $P/A = \varepsilon\sigma\ (T_{TUMOR} - T_{SINK})^4 = (10V)(50\ mA)/\pi(0.01)^2 = (1)(5.67 \times 10^{-8}\ W/m^2\ °K)\ (T_{TUMOR} - 300\ K)^4$.

   Therefore, T_{TUMOR} = 710K or approximately 1,260°F. Hot! Hot! Hot! As one would expect, radiation is not very effective as a primary heat transfer mechanism. Maybe we should consider heat loss by *conduction*:

$$(\Delta Q/\Delta t) = (k)(\text{Area})(T_{TUMOR} - T_{BODY})/(\text{length})$$

$$(10\,V)(50\ mA) = 0.5W =$$
$$0.119 \times 10^{-3}\ Cal/sec =$$
$$(1.45 \times 10^{-4}\ Cal/sec\ m°C)$$
$$(3.14 \times 10^{-4}\ m^2)(T_{TUMOR} - T_{BODY})/(0.01m)$$

   Therefore, if T_{BODY} is 27°C, T_{TUMOR} would be 53.14°C, or 127.6°F. That is still a bit warm. But it is not too far away from localized

temperatures associated with hyperthermia treatment for isolated tumors. So, now, we might consider *convection*:

$$(\Delta Q/\Delta t) = (14.5)(\text{Area})(v_W)^{1/2}(T_{TUMOR} - T_{AMBIENT})$$

where v_W is an effective velocity for still air: (10V)(50 mA) = 0.119×10^{-3} Cal/sec = $(14.5)(3.14 \times 10^{-4}\ \text{m}^2)(0.23\ \text{m/sec})^{1/2}$ ($T_{TUMOR} - T_{AMBIENT}$). Therefore, the difference between the tumor temperature and ambient ($T_{TUMOR} - T_{AMBIENT}$) is very small (approximately 0.17°C). Heat loss by evaporation is also a significant factor in controlling temperature at body surfaces. Conduction and convection would probably be the dominant factors in localized tumor temperature control for the electrotherapeutic treatment of lung malignancies. However, it would appear that convection and evaporation heat loss mechanisms would be less dominant for internal cancer (liver, bladder, brain, and so on). For these internal locations, conduction would become the primary tumor heat loss mechanism. Considering conduction only, the previous calculations imply that temperature increases associated with power absorbed by internal tumor sites could be significant. However, as long as the tumor temperature increases do not become too extreme, the additional hyperthermia contribution from the elevated tumor temperature could enhance therapeutic efficacy for the electrotherapeutic technique applied (in this case, NEAT-EChT). This analysis using various heat transfer models is a bit flawed because it assumes the 10-V applied source voltage drop is uniform. A large part of the supply voltage is dropped at the electrode-tissue interface due to a number of nondissipative mechanisms including polarization effects that occur at dc, or at very low frequencies. Another flaw in this analysis involves differences in current densities and voltage drops near the center region of the tumor compared with the outer periphery of the tumor. If the center of the tumor is more of a liquid matrix compared with the periphery, the power dissipation and temperature could be somewhat different at the center of the tumor compared with the peripheral regions of the tumor. During NEAT-EChT, the tumor is not a simple homogenous entity from the standpoints of electrical processes, material mix, chemical activity and structure.

9. (a) Using a somewhat simplified approach, I get a slightly lower number. In order to keep it simple, I assumed a simple cubic structure for the atoms in tissue, with an atom at each corner. Each corner atom is spaced at an average distance of 2.5Å (2.5×10^{-10} m) from its nearest neighbors at the other corners. Since each corner atom is shared with

eight neighboring cubes, there is one atom per cube in this structure. The volume of each cube would be 15.625×10^{-30} m^3. So the number of atoms in our body (N_{BODY}) can be estimated:

$$N_{BODY} \approx (1\,\text{Atom/cube/Volume per cube})$$
$$(\text{Human tissue volume}) =$$
$$\left[(1)/\left(15.625 \times 10^{-30}\,\text{m}^3\right)\right]\left(0.037\,\text{m}^3\right) =$$
$$\underline{2.368 \times 10^{27}\,\text{atoms}}$$

(b) If we assume 5T tissue cells per body, the number of atoms per tissue cell ($N_{TISSCELL}$) will be

$$N_{TISSCELL} \approx (\text{Atoms per body})/(\text{Cells per body})$$
$$= \left(2.368 \times 10^{27}\,\text{atoms per body}\right)/$$
$$\left(5 \times 10^{12}\,\text{Cells per body}\right) =$$
$$\underline{4.74 \times 10^{14}\,\text{atoms per cell}}$$

(c) The presence and ratios of most of the elements in our bodies indicate that, as many astronomers and cosmologists maintain [11], we are made of stardust, or that we are made up of material from ancient supernova activity. This is a delightful concept to some, and very irritating to others. The NASA Goddard Space Flight Center Web site has an interesting comment on this. In the "Ask an Astrophysicist" section. They mention that the "we are all star stuff" statement became quite popular from comments made by the late Carl Sagan. They also mention the Joni Mitchell Woodstock song that contains the words, "We are stardust, we are golden, we are billion year old carbon and we've got to get ourselves back to the garden." Crosby, Stills, Nash and Young have a rock version of the song. No matter which version you prefer, this song provides the listener with an interesting blend of astrophysics, biochemistry and poetry.

Chapter 2

1. Assume charge is moving in the x direction: $\Delta Q = (\rho_{CH})(\Delta\text{Volume}) = (\rho_{CH})\ (A\Delta x)$. $I_X = \Delta Q/\Delta t = (\rho_{CH} A\Delta x)/\Delta t = \rho_{CH} A v_D$. Now, $(\rho_{CH}) = pq =$

pe (where p represents the number of carriers per volume) and $q = e$, the charge on the carrier. Therefore, $\underline{J} = I_X/A = (\rho_{CH})(v_D) = \underline{pev_D}$.

2. If d is the electron mean free path between collisions, and motion is in the x direction, from (2.4), $F_X = q\mathrm{E}_X = ma_X$. $v_{DX} = \mu \mathrm{E}_X$, $J_X = (\rho_{CH})(v_{DX})$, where v_{DX} represents the average velocity for electrons that are accelerating in an electric field, stopping abruptly after a collision at each mean free path increment (d) and then repeating the process again. Since this exercise is associated with electron flow, I should have a negative sign associated with the current density because the electron is moving in the opposite direction to conventional current flow. But I will ignore the negative sign.

   Therefore, since $J_X = (\rho_{CH})(v_{DX})$, $J_X = (\rho_{CH})\mu \mathrm{E}_X = (pe)\mu \mathrm{E}_X = (pe\mu)\mathrm{E}_X = \sigma \mathrm{E}_X$ [from (2.6)] $= (1/\rho)\mathrm{E}_X$, where σ represents conductivity and ρ represents resistivity. $\mathrm{E}_X = V_X/\mathrm{l}$, where l is the length of the conductor.

$$I_X = AJ_X = (A)(1/\rho)\mathrm{E}_X = (A)(1/\rho)(V_X/I)$$
$$V_X/I_X = (\rho)(I/A) = R \quad (\text{Ohm's law})$$

3. Ah, the energy "thing." It seems to be the bear trap that constantly gets in our way. In this case, $|G^{O'}| \geq$ (2/mol)(23 kcal/V)(0.218V) $\approx$ 10 kcal/mol. The endogenous and exogenous potential differences within the cellular volumes are much lower than 0.218V. We must keep in mind that $V^{O'}$ is an oxidation-reduction potential associated with chemical activity and chemical reactions associated with breakdown and synthesis. We do not need high-energy mechanisms to have significant influences on chemical activity. The relatively low energy level electrical activity associated with ionic current flow (promoted by endogenous and exogenous voltage sources or potentials) is instrumental in transporting ions, polarized molecules (water) and charged molecules toward, or away from, the sites where they are utilized in chemical synthesis or chemical breakdown reactions. The movement and accumulation of charge in certain regions of the cell can also have significant impacts on chemical activity in cell signaling pathways. In addition, the movement of water and variations in pH influenced by endogenous and exogenous sources can have significant impacts on chemical activity. The type of endogenous and exogenous electrical activity described in this book involves fairly subtle energies. Also, even with small potentials, the flow of current can promote charge accumulation in certain cellular locations, and influence structure and function associated with certain cell membrane components. In fact,

certain cell membrane structures can be moved under the influence of an applied electric field.

4. From the standard free energy expression in Exercise 3, the use of the standard at a pH of 7 is a strong indicator that pH has an influence on the energies associated with chemical reactions. In fact, reaction rates for enzyme-catalyzed reactions are affected significantly by both pH and temperature levels. Many enzyme-catalyzed reactions exhibit a "window" of optimum activity over a range of pH and temperature values. The measurement of blood pH is useful in determining the pulmonary system's ability to remove CO_2 from the body and regulation of the acid-base balance by the renal system. Also, (2.5) indicates that skin potentials can be influenced significantly by pH differences between certain tissue layers or tissue-organ locations.
5. In his book, *Biologically Closed Electric Circuits*, Nordenström describes four different electro-osmotic transport mechanisms [12]. In type III electro-osmosis, he describes the behavior of positively charged ions migrating in the electropositive region of an electric field (for instance, near the center of a necrotic tumor or a wound site). Water molecules are adsorbed on the surface of the positively charged ion. In this region, water molecules do not attach themselves to negatively charged ions. As the positive ions move, they carry adsorbed water molecules along with them, and electric field–assisted electrophoretic water transport occurs in one direction.
6. Think about your microwave oven. Using a magnetron source, it directs microwave radiation at a frequency of approximately 2.5 GHz. The microwave radiation has a very low photon energy (16.5×10^{-25} J or 10.25×10^{-6} eV), which is much too low to ionize molecules from a photon energy standpoint. However, let us consider a magnetron source output power of 700W. If the assumption is made that no heat escapes from the food item being irradiated, the specific heat relationship can be used. A 0.6-kg item of food is left in the microwave oven for 10 minutes (600 seconds). The specific heat for the food item can be considered close to that of water. 700W is equivalent to 0.167 Cal/sec and the ambient temperature is assumed to be 30°C:

$$T_{FOOD\ ITEM} - T_{AMBIENT} = (\Delta Q)/(\hat{C})(\text{mass}) =$$
$$(0.167\ \text{Cal/sec})(600\ \text{sec})/(1\ \text{Cal/kg}\,^\circ\text{C})(0.6\ \text{kg}) = 167^\circ\text{C}$$

This temperature is high enough to affect protein folding (frying an egg, which involves the unfolding of proteins) and to cook meat and

vegetables. The high voltages (up to 4.5 kV) and relatively high magnetic flux densities (up to 0.1T) utilized by the oven magnetron can produce very high electric field intensities and magnetic field intensities in the device. The output power and energy supplied by the magnetron are a function of the electric field intensity, magnetic field intensity, and cross-sectional area associated with the magnetron device and the output radiation characteristics. In this case, the energy and power supplied by the magnetron are a function of the intensity of the radiating electromagnetic field components. The power absorbed by the biological material is also a function of frequency, the imaginary part of the complex dielectric constant, and the RMS electric field intensity [$P = (2\pi f)\ \varepsilon_O \varepsilon_I E_{RMS}^2$ (volume)]. So the energy associated with the interaction of an electromagnetic wave and a biological system at microwave frequencies would involve the absorption and accumulation of energy from an electromagnetic source (magnetron). The accumulation of energy causes an increase in heat energy that results in a temperature increase (if the heat is not transferred by radiation, convection, or conduction). Microwave radiation has been used in cancer therapy to raise tumor temperature to a higher level than the surrounding tissue. This technique is called hyperthermia. The power absorbed can be higher for the tumor due to a larger dielectric constant value for tumor tissue (see the previous absorbed power expression). The tumor cells are most sensitive to hyperthermia during the S-phase of the cell cycle when new DNA is being synthesized. High temperatures can damage the poorly formed malignant cell membranes by denaturation. Also, at higher temperatures, the tumor's poorly formed vascular system is compromised and blood flow to various parts of the tumor is inhibited. This inhibits the flow of oxygen and nutrients to specific regions of the tumor. Inhibiting blood flow in the tumor also interferes with heat transfer, resulting in higher tumor temperatures.

Infrared radiation involves frequencies and wavelengths that can interact with the molecular vibrational modes that occur between groups of atoms. For instance, using the photon energy relationship of $E = hf$, an infrared photon with a wavelength of 1.239 μm (or a frequency of 2.42×10^{14} Hz) would have a photon energy of 1 eV or 1.6×10^{-19} J. One mole of these 1.239-μm infrared photons would have an energy of approximately 23 Cal/mol, or 23 kcal/mol (How did I get that number?). Breaking C-N and C-C bonds requires 70 kcal/mol and 83 kcal/mol, respectively. The 1.239-μm wavelength infrared photon energies are not high enough to break covalent bonds (generally, requiring energy levels of 50 kcal/mol or higher) in biological tissue. However, infrared frequencies are high enough to interact with

molecular vibrational modes between groups of atoms, and if the frequency is the same as the vibrational mode frequency, the infrared energy will be absorbed. This is the basis of infrared absorption spectroscopy. Over a range of infrared wavelengths or frequencies, each molecule will have its own unique absorption pattern, and this pattern can be used to identify the presence of specific molecules in a sample.

As we make the transition from the infrared and visible light spectrum into the world of ultraviolet light (with wavelengths equal to or less than 400 nm, and frequencies of 7.5×10^{14} Hz or higher), the photon energies associated with these wavelengths and frequencies are high enough to break various carbon bonds of biological tissue. With respect to cancer, ultraviolet light can be a cause (DNA dimer formation/gene mutations), a diagnostic tool (UV photography), and a treatment modality (UV photodynamic therapy).

Certain frequencies in the ultraviolet light spectrum are the same as the vibrational frequencies associated with electrons that are bound to atoms. The energy of an ultraviolet photon can be absorbed when it interacts with a bound electron that has the same vibrational mode frequency. This is the basis for ultraviolet absorption spectroscopy.

Gamma rays and X-rays have significantly higher frequencies and significantly higher photon energies. It is interesting to note that, with respect to cancer, X-rays can be both a cause (mutations and activation of oncogenes) and a treatment (by breaking DNA bonds in rapidly dividing malignant cells during mitosis).

7. In the multistep process of healing, the activity of dermal cells and epidermal cells is described in [13, 14]. For intact skin, cells are bathed in plasma. But when wounded, the cells at the wound site are exposed to serum. Serum is the clear liquid that can be separated from clotted blood. The primary difference between plasma and serum is that serum has no clotting factors.

   Wound healing requires migration of the appropriate cells. Human serum apparently promotes the migration of epidermal cells and inhibits the migration of dermal cells. The change from plasma to serum is associated with inflammation. How would electrical processes influence the migration of appropriate cells, the transition from plasma to serum, and the transition back again to plasma during the wound healing process?

Chapter 3

1. There are a variety of useful mechanical and fluid analogs for electrical circuits. Kirchhoff's equation, where the sum of the voltages around a

series electrical circuit is equal to zero, is the analog of d'Alembert's equation for mechanical systems, where the sum of the forces on a simple series mechanical system is equal to zero. A force, *F*, is analogous to a voltage, *V*. Displacement, *x*, is analogous to electrical charge, *Q*. Velocity, *v*, is analogous to electrical current, *i*. Viscous friction, *D*, is analogous to electrical resistance, *R*. Mass, *m*, is the analog for inductance, *L*, and the spring constant, *K*, is the analog to capacitance. A voltage in series with a number of different resistances (similar to a simple BCEC circuit) is the analog to a mechanical system with a series of cylinders of different length (and negligible mass) sliding in a tube where viscous friction is dominant. The equations for the analogous electrical and mechanical systems will have the same form, with different units.

Consider a pump that pulls water out of a pool and is connected to a series of pipes of different diameter and length. The water finally exits the last pipe and splashes back into the pool. This would be the fluid analog to the simple series electrical circuit. In this case, the pump output pressure would be analogous to voltage, the resistance to flow of the different pipes would be analogous to electrical resistance, the volume flow of water would be analogous to electrical current and the pool level would be analogous to an electrical ground.

2. (a) No! If we had electrons traveling at the speed of light in us, we would glow in the dark. From a relativistic effect standpoint we would be enormously heavy (like, infinitely heavy) and there would not be enough food to feed us.

   (b) We can see from the equations involving current density and, mobility, charge density, average velocity, etc. that the average velocities for charged carriers in conductors are very low (often in the millimeter per second range). Instantaneous velocities, or Fermi velocities, for electrons in many metals are much higher, in the range of 1×10^6 m/sec to 2.5×10^6 m/sec (see [15]). These are high velocities, but they are approximately 100 times lower than the speed of light. While under the influence of an electric field, electrons transport is directed, but the electrons are scattered by a variety of mechanisms (Coulomb interactions, atomic lattice sites, various types of defects). One can use the analogy of a traffic jam where a large number of vehicles in a confined pathway are changing lanes, avoiding obstacles, and swerving back and forth very fast over short durations, but still the overall traffic speed in the forward direction is very slow. Similarly, the resulting average or forward drift velocities that occur with the application of an electric field are much lower than the instantaneous velocities or Fermi

velocities. The orbital velocities of electrons associated with various atoms are also considerably lower than the speed of light. Using either the Rydberg constant or a simple force-energy relationship, $v_O = q^2/\varepsilon_O 2nh$, orbiting electron velocities associated with atoms (v_O) are approximately 2.5×10^6 to 5×10^6 m/sec.

Now, consider a very thin insulating film deposited on a metal, with another metal deposited on top of the insulating film (a metal-insulator-metal structure). Generally, the energy barrier between an insulator and a metal is so high that no electrons can flow from the metal through the semiconductor. But, if the insulating film is thin enough, a voltage applied across the film can produce a huge electric field. If the insulating thin film is 250Å thick (25 nm), and 2V is applied, the electric field (E) in the insulating film is a whopping 80 MV/m! For electric fields of this magnitude, the energy barrier (Schottky barrier) is lowered and some of the high-energy conduction electrons are transported across the insulator from the negatively biased metal to the positively biased metal counterelectrode. If the insulating film is much thinner, electrons can tunnel through the energy barrier and be transported to the metal counterelectrode. In Chapter 2, (2.4) provides a useful relationship for this question ($Force = q\mathrm{E} = mdv(t)/dt = ma$, and velocity is given as the mean free path divided by the time between collisions). If the ballistic model is used, and a mean free path between collisions of 4Å is assumed, the time between collisions is approximately 0.53×10^{-14} sec (reasonable) and the peak velocity is approximately 0.75×10^5 m/sec. Conduction electrons at these velocities are often referred to as *hot electrons* because they have much higher velocities and energies compared with electron transport velocities in conventional conduction mechanisms.

3. If the boundary layer thickness, d, is considered to be approximately $0.03R$ and area, A, is approximately equal to πR^2, the right side of Equation 8 is approximately 1.8 times larger in magnitude compared with the equation derived using Stoke's law. The primary difference between the two equations is that the Stoke's law version is more rigorously derived from fundamental relationships. The other version is derived by simply relating the force on a charge with the force on a spherical cell moving in a viscous fluid.
4. (a) The current in a single ion channel might be in the range of 0.4 pA over a 3-μs interval for calcium ions [16] and up to 40 pA for a single ion channel fluctuation [17]. In addition, a single acetylcholine (ACh) channel associated with a nerve synapse might have 2.5×10^7 ACh ions/sec flowing through an open channel with dimensions of 48 nm $\times$

48 nm × 32 nm, with a channel membrane voltage of –100 mV. Considering ACh having a +1 charge, the resulting current would be 4 pA. With approximately 15,000 ACh ions available, this current would occur over a time frame of approximately 600 μs with the highest activity occurring over a time period of approximately 13 μs.

(b) For a cell, the number of ion channels per square micrometer is often given in the range of 100 to 400 (this channel density can be significantly higher for nerve synapses). So, a simplified and isolated spherical synaptic cell with a 20-μm diameter could have approximately 125,600 to 502,400 membrane ion channels of various types and sizes.

(c) If all of the ion channels were in operation, and if the average ion current flow was 2 pA, the total current per cell would be approximately 0.25 to 1 μA at a current density of 20 to 80 mA/cm^2. The current density estimations seem to be much too high compared with the 1-mA/cm^2 current density that has been given previously. So, if approximately 4.5% of the cells in the body were considered to be strongly active and only 2.5% of the ion channels on each cell were in operation at one time, that would bring the current density range and metabolic rate down to reasonable levels.

5. This problem is not as esoteric as it may seem. Tunneling appears to be a factor in the *catalytic power* for certain enzyme-catalyzed reactions, photosynthesis, and respiration. Short and long-range electron transfer, proton transfer, and oxidation reactions are affected. The ability for a charged particle to tunnel will be a function of how the width of the energy barrier relates to the de Broglie wavelength of the charged particle. An examination of the de Broglie wavelength equations shows that the de Broglie wavelength (λ) can be expressed in a number of different ways for the electron and proton: $\lambda = h/mv = 2\pi/k$. In these equations, we have Planck's constant, h, mass, m, velocity, v, and wave number, k. If the energy of the electron is in eV, the de Broglie wavelength can be expressed as: $\lambda = 12/(E(\text{eV}))^{1/2}$ (Å). So a conduction electron with a 0.3-eV energy would have a de Broglie wavelength of approximately 21.9Å. A conduction electron with a 1-eV energy would have a de Broglie wavelength of 12Å. In metal-insulator-metal thin film structures, if the insulating film thickness is 100Å or less, and if a voltage of 1V is applied across the insulating film, the width of the energy barrier near the conduction band is close to the de Broglie wavelength of the higher energy conduction electrons (< 20Å) and electron tunneling through the insulating barrier has a relatively high probability of occurring. So for electronic devices, conduction electron

energies of 0.3 eV to 1V would involve tunneling distances of approximately 12Å (distances between atoms are often in the range of 1.5Å to 3.5Å).

The de Broglie wavelength for a proton with an instantaneous velocity of 10^4 m/s is approximately 0.41Å. For certain reactions, Masgrau et al. [18] indicate tunneling energies of 8.7 and 10.4 kcal/mol. Converting to electron volts for a single proton, energies of 0.38 eV to 0.47 eV are calculated:

$$\begin{aligned}&(8.7\ \text{kcal/mol})(4{,}184\ \text{J/kcal})/\\&(6.02\times10^{23}\ \text{protons per mol})\\&(1.6\times10^{-19}\ \text{J/eV}) = 0.378\ \text{eV/proton}\end{aligned}$$

Tunneling distances associated with electron transfer events in protein-protein interfaces and nucleic acids appear to involve distances of 4Å to 14Å, with electron energies close to 1 eV [19, 20]. These values for electron transfer tunneling mechanisms in certain chemical reactions appear to be close to the tunneling distances involved with electron transport in certain types of thin film electronic devices. For protons, the process and probabilities associated with tunneling in chemical reactions appear to involve distances that are significantly less than tunneling distances associated with electrons in chemical reactions and thin film electronic device structures.

Chapter 4

1. Ampere's circuital law provides an expression that specifies a magnetic field with every current. On an atomic scale, orbiting electrons or spinning electrons (or spinning charges) could be thought of as "currents" on a much more microscopic level. An orbiting or spinning electron will possess a magnetic dipole moment that is normal to the orbital or spin angular motion. Paramagnetism requires permanent magnetic dipoles.

   In paramagnetism, the magnetic dipoles are randomly oriented in the absence of any outside stimulation. The energy associated with room temperature activity (kT) is more than enough to maintain random dipole orientations for the weakly interacting magnetic dipoles so that there is no net magnetic effect. However, if an external magnetic field is introduced, some of the weakly interacting magnetic dipoles

will align themselves with the applied magnetic field. The susceptibility of a paramagnetic material is small and positive, producing an attraction affect.

The magnetic moment of a free atom has three primary sources: electron spin, electron orbital angular momentum, and change in orbital moment induced by an applied magnetic field. The first two effects contribute to paramagnetism. The third provides a diamagnetic contribution (see [15]). In a diamagnetic material, the orbiting electrons exhibit precession with an applied magnetic field (Larmor precession). This is similar to the precession associated with a spinning top when it is pushed slightly from the side. The diamagnetic susceptibility of an isolated atom is a function of the mean squared distance of the distribution of electrons from the center of the nucleus (Kittel). The susceptibility of a diamagnetic material is small and negative, producing a repulsion effect. Diamagnetic substances are repelled by the poles of a conventional magnet.

Give this some thought. What is the basic difference between paramagnetism and ferromagnetism? The ferromagnetic effect is more than a million times stronger than the paramagnetic or diamagnetic effect. Why is the ferromagnetic effect (like the effect you experience with bar magnets) so strong compared with the very weak paramagnetic effect?

The July 22, 1999, issue of *Nature* [21] shows a tiny but very strong NdFeB magnet levitating between a thumb and index finger positioned several meters under a superconducting magnet. As the small magnet starts to fall under the influence of gravity, the diamagnetic effect associated with moisture in the thumb repels the magnet (water is diamagnetic). This tends to push the magnet up, counteracting the force of gravity. However, the small magnet can only go so far because the diamagnetic effect of the finger above the thumb also repels the tiny magnet. So the object levitates at a point where the two opposing repulsive forces associated with the diamagnetic effect balance out with the downward force of gravity.

2. A paper written by Kobayashi, Yamamoto, and Kirschvink in the *Journal of the Japan Society of Powder and Powder Metallurgy* [22] provides some interesting insights on this topic. Ferromagnetic material has been extracted from magnetotactic bacteria, mollusks, fish, and the human brain. A wide range of malignant tumor tissues (melanoma, breast cancer, ovarian and testicular cancer, sarcoma, meninginoma, glioblastoma, astrocytoma) also show evidence of magnetite (Fe_3O_4) and irregular patterns of ferritin. The hydrated iron oxide in ferritin has been suggested as a possible precursor to the magnetite detected in

some organisms and tissues, but it may not be the magnetite source in others. The presence of magnetite in bacteria, fish, and birds may be associated with the use of the Earth's magnetic field in orientation, migration, and navigation. The presence and distribution of magnetite in the brain is being evaluated with respect to its potential role in neurological diseases such as epilepsy and Parkinson's disease. Also, increases in iron levels have been associated with cancer and diabetes. Ferritin appears to play a role in the proliferation of malignant cells for various types of cancer conditions.

3. Detecting the presence of iron compounds in tissue samples could be accomplished using staining techniques and an optical microscope if the particles are large enough. This would be a relatively low-cost approach. For higher magnifications and better resolution, very thin slices of tissue could be prepared for transmission electron microscopy (TEM). The well-defined crystal faces associated with the iron compounds will be easy to see and differentiate with respect to other tissue structures. A TEM system is quite expensive, and tissue sample preparation for TEM studies is much more complicated than simple staining techniques associated with optical microscopy. Kobayashi, Yamamoto, and Kirschvink [22] used a superconductive quantum interference device (SQUID) magnetometer to measure the magnetic parameters of the iron compounds in various tissues. They were able to accomplish this using only liquid nitrogen.
4. Well, what is your opinion on this one? There are all kinds of hand-waving explanations for this question, but I have not heard one yet that I really like. A 1T magnetic field is one hundred billion times more intense than a 10-pT magnetic field. If a 10-pT magnetic field produces a therapeutic effect for Parkinson's disease and epilepsy patients, why doesn't a 1T magnetic field either exhibit an enhanced effect in treating these two diseases, or completely traumatize the patients neurological system? There is evidence of a window effect here. The lower magnetic field intensities appear to influence transport mechanisms associated with charged entities at synaptic junctions and in the region of cell membrane ion channels. The higher magnetic field flux densities appear to be more influential with gross changes in nerve cell membrane polarization and action potentials.

   At low frequencies, the 1T magnetic field has proven to be useful in the treatment of depression (repetitive transcranial magnetic stimulation, or rTMS). The 10-pT magnetic field has also been helpful for a number of Parkinson's disease patients in relieving their depression problems. The mechanisms associated with the relief of depression are

probably somewhat different for the 1T and 10-pT magnetic field flux densities. Subthreshold 20-Hz rTMS appears to have an increase in corticospinal excitability and motor response, while the lower 1-Hz rTMS appears to reduce motor response (see [23]). Also, brain plasticity (the brain's ability to compensate for lost function) appears to occur at both the 1T rTMS level as well as the 10-pT pT-MT level (see [24, 25]).

5. Lai and Singh [26] reported DNA strand breaks at magnetic flux densities of 0.1 to 0.5 mT at 60 Hz. Since magnetic fields at this level do not have the strength to break chemical bonds directly, they proposed that the 60-Hz magnetic fields affect enzymatic processes (possibly poly-ADP-ribose polymerization) involved in DNA repair, leading to an accumulation of DNA strand breaks.

   An interesting direct interaction mechanism has been proposed by Blank [27] that proposes a direct interaction between a magnetic field and the electrons flowing along the DNA strands. As we have previously indicated, there appears to be a considerable amount of electron transport activity in DNA. The force produced by the combination of the current, I, that involves electron flow and the magnetic field with flux density, B, along a strand segment, L, would be: $F = (B)(L)(I)$, assuming that the flux density and current are at right angles with respect to each other. With a high enough magnetic flux density, the force on each strand could cause a set of repulsive forces between them, producing a bend or possible break in the strand pair. Blank and Goodman take this idea a bit further and propose that weak low-frequency electromagnetic fields interact directly with DNA due to relatively large magnitude electron flow in the stacked base pairs of DNA [28]. Adair takes issue with this proposal and claims that weak electromagnetic fields cannot interact directly with DNA [29]. More detail on this subject appears in Chapter 5.

6. If you can answer this question, please tell everyone how much this book inspired you as you accept your Nobel Prize. Some of the factors and potential promoters associated with Parkinson's disease are mentioned in Section 4.3. In one of their studies on Parkinson's patients, Anninos et al. [25] indicate that a number of possible electrophysiological explanations have been proposed for the efficacy of pT magnetotherapy. One possibility involves a neural net model that suggests magnetic stimulation causes temporary neuronal inhibition (of the offending neural complex). Another possibility involves the effect of magnetic field on pineal gland activity and that particular gland's regulation of dopaminergic functions. They mention Morrell's

hypothesis of persistent stimulation (magnetic in this case) that is eventually converted from a short-term memory to permanent memory (a plasticity mechanism). The effects of magnetic fields on the properties and stability of cell membranes and transport characteristics (including calcium ion transport) may have an effect on mitigation seizure activity. Other papers have discussed magnetite-facilitated mechanisms for epilepsy.

Chapter 5

1. The wave function momentum representation for an electron, $(h/2\pi)k$, is quite different from the momentum expression for the particle version of the electron (mv). The thermal excitation frequency of the electron in this model is approximately 0.64×10^{13} Hz, the wavelength of a room temperature electron (0.026 eV) is approximately 75Å, and the Fermi velocity is approximately 4.8×10^{4} m/s. With Planck's constant being 6.6×10^{-34} Jsec, the wave function momentum is about 8.8×10^{-26} Jsec/m. Assuming the rest velocity mass of 9.1×10^{-31} kg for the electron, the momentum for the electron as a particle is about 4.36×10^{-26} kgm/sec (Check the units! Is a Jsec/m equivalent to a kgm/sec?). There is a difference between the momentum terms, and the ratio is approximately two. If we compare the energy expression for a wave function ($h\nu$) with the kinetic energy expression for a particle ($mv^2/2$), the wave function energy is approximately 4.2×10^{-21} J and the particle energy is approximately 1.1×10^{-21} J. The difference between the two energies involves a ratio of 3.8. Obviously, there are momentum and energy differences associated with the way the electron is modeled. In the wave function model, we have also assumed that the instantaneous, phase, and group velocities are all the same. That is often not a very accurate assumption, especially as the energy level of the electron increases. Also, the wave function model does not provide a mechanism to account for the effective mass of the electron. In conductors and semiconductors, the effective mass can be quite different in magnitude compared with the rest mass.
2. This was an attempt to relate a resonance phenomenon at pT magnetic field levels by relating Einstein's equation with the Lorentz force. The conceptual problem with this approach is that it tries to relate a *very* high energy expression (mc^2) with a *very* low energy expression (qBv_GL). By taking some typical values of mass, group velocity, charge on the electron, a 10- to 20-pT magnetic flux density, and a reasonable

value for electron mean free path ($L \approx 10$Å to 400Å). Are the two sides of this equation a little out of balance?

In order to make this approach work, the individual who developed the expression for f_R apparently changed the value of the electron charge (1.6×10^{-19} C) to a normalized value of 1C. In one part of the derivation, the electron velocity term is equal the speed of light. In another part of the derivation, the group velocity term is related to the Earth's rotational velocity. Cellular or human body dimensions are used for the length variable. Then, when the resonance frequency term is derived, the magnitude of the normalized charge of the electron changes from the normalized value of 1C back to 1.6×10^{-19} C. The person who developed this theory has done some reasonably good work in the area of magnetotherapy. I gave a paper at a conference in Montreux, Switzerland that critiqued his theory and assumptions. Needless to say, it was not a pleasant experience for either of us.

Chapter 6

1. Meaningful and reasonable analytical results require a realistic starting point. Assumptions provide the starting point and a direction for an analytical effort. If the assumptions are wrong, the accuracy of the analytical results and relevancy of the conclusions will be in doubt. As an example, a business forecast for new orders, sales, and profitability for the next 3 years might vary considerably if different assumptions or different scenarios are considered. The forecast will probably be much better under the assumption that the economy will be healthy, interest rates will remain relatively low and consumer confidence will continue to rise over the next 3 years versus the assumption that the economy will be stagnant, interest rates will be increasing, and consumer confidence will be decreasing during that time.

   As you make a turn at a green light, you may want to look both ways just to make sure no one is running the red light. Don't look only in the direction you are turning and assume that everyone else is alert and has the sense to stop. The devil is definitely in that assumption. The first two pages of Chapter 8 discuss an assumption that was made concerning an electromagnetic interference problem. In this case, the people who were trying to solve the interference problem initially assumed the interference was due to the equipment. We often fall into the bad habit of assuming that the equipment is the source of the problem, when in many cases the source of the problem might be the equipment operator. In a *Dilbert* cartoon by Scott Adams, Dilbert tells

his boss, "I can do this feasibility analysis in two minutes. It's the worst idea in the world. Numbers don't lie." Dilbert's boss says, "Our CEO loves the idea." Dilbert thinks a moment and then replies, "Luckily, assumptions do lie." Well, in that cartoon, we see evidence of the "devil," again.

2. After examining a number of patents that fall under this category, I have the impression that many patent holders are not aware that they could have serious infringement and legal problems if their patents are scrutinized. Patent claims can be declared invalid if they incorporate features that are obvious in view of prior art. Also, for a patent that has been filed and approved, if the patent is based on technology or prior art that the patent holder knew was publicly available and did not disclose, the patent holder could be found guilty of fraud (see [30]).
3. Considering the rather large number of mechanisms proposed for the therapeutic efficacy of NEAT-EChT, the patent holder would appear to have the biggest problem. By not including a reasonable number of potential therapeutic mechanisms, the patent could be invalidated. Basing the therapeutic effect of a biomedical device patent claim on just one mechanism is risky, especially if the proposed mechanisms are still being debated.
4. Some patent lawyers are concerned that the Supreme Court might scale back the kinds of ideas that can be patented in an effort to protect innovation while trying to avoid hindering commerce. The Supreme Court may also have to set a ruling on what constitutes "obvious" in patent applications (see [31]). Some of the most interesting courtroom patent warfare involved the combined efforts of the Federal Trade Commission (FTC) and a number of semiconductor companies to invalidate patent claims made by Rambus (licenses computer memory chip designs). It is an interesting, long, and very disturbing story. But in its dealings with the Rambus patent and licensing issues, it does appear that the FTC's tactics were very unusual, if not inappropriate.

   Several companies have accused Rambus of violations of the Racketeer Influenced and Corrupt Organizations (RICO) Act. However, some of the companies making those accusations have been found guilty of violating antitrust laws (in this case, collaborating and participating in price-fixing schemes). One of the companies that apparently participated in the price-fixing schemes was given immunity for its cooperation with the Antitrust Division of the Justice Department. On June 1, 2006, Reuters revealed the content of e-mails that were sent by two of the companies that have attempted to charge Rambus with RICO violations [32]. Apparently, the e-mails show that these

companies were collaborating (trading information) in an effort to keep prices high on one set of memory chip products. They also appear to have attempted to keep prices low on another memory chip product line in order to discourage the use of a Rambus technology.

The AC/DC song "Dirty Deeds, Done Dirt Cheap" keeps playing over and over in my mind.

5. Before looking back, just think about the safety concerns you would have if you were going to treat your own eyes with an electrotherapeutic device. Going a little further, what kind of concerns would you have if the device was a laser?

Chapter 7

1. The equation for the electrode (redox) potential will have the same form as the Nernst equation.
2. Assuming charge formation on the surface of a metallic electrode in an electrolyte, and charge formation on the surface of a dielectric colloidal sphere in liquid, the model for the various layers and potential drops as a function of distance are quite similar for the electrode and colloidal particle. The electrode and colloid models both have a double layer consisting of a Stern layer (less than 1 nm in thickness from the surface) and a diffuse layer (approximately 10 nm thick). The Stern layer is associated with the region where counterions are attached to the surface of the electrode or colloidal particle. An additional group of ions is associated with the electrode or colloid surface close to the counterions. The region between this layer and the liquid is referred to as the *shear plane*. The electrical potential associated with the shear plane between the liquid and the charges associated with the surface and near-surface of the electrode or colloid is defined as the *Zeta potential*. The Zeta potential is directly proportional to the charge associated with the Stern layer and the double layer thickness. It is inversely proportional to dielectric constant. The characteristics of the potential drop with distance for electrodes and colloidal particles are quite similar in form.

   With changes in pH, (2.5) in Chapter 2 indicates that magnitude of the electrode potential will increase (with respect to its 0 reference voltage) in the positive direction. The effect of pH on colloidal particles is somewhat complex and nonlinear for substances such as minerals, ores and ceramics. However, in biological systems, a reduction in pH to a more acidic level will often cause the Zeta potential of certain

molecules and cellular components to decrease. As Zeta potential decreases, these substances will tend to clump or aggregate. This is a desirable feature if one wishes to bring suspended particles out of solution. But clumping or aggregation can be deadly in the human body, especially in the cardiovascular system. Small reductions in pH can lead to cardiovascular failure (via coagulation, atherosclerosis, thrombosis, and so on). It would appear that lifestyle and nutritional choices that maintain control of pH levels might be good things to consider.

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