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

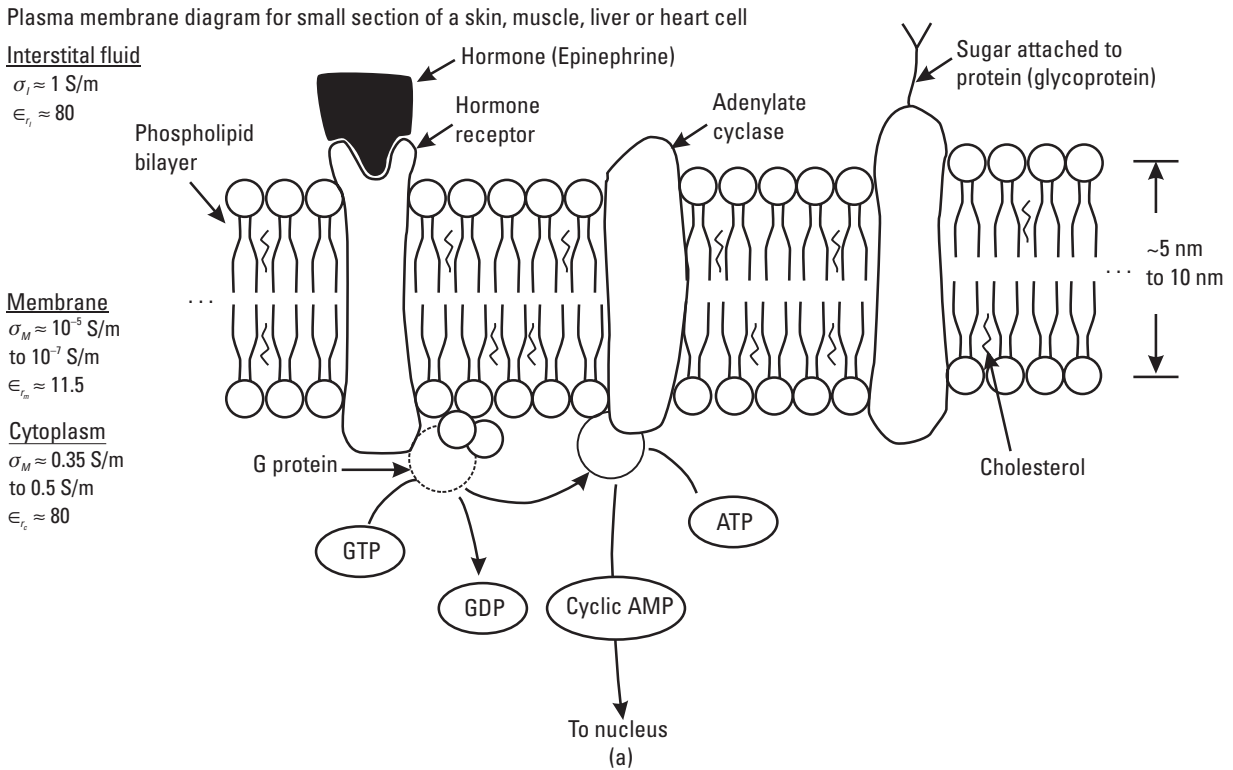


Figure 3.1 (a) Surface and near-surface region of a eukaryotic cell showing structures that contribute to the cell's electrical properties and electrical response along with part of a signal transduction pathway involving cyclic AMP. (b) Possible cell membrane receptor response to electrotherapeutic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

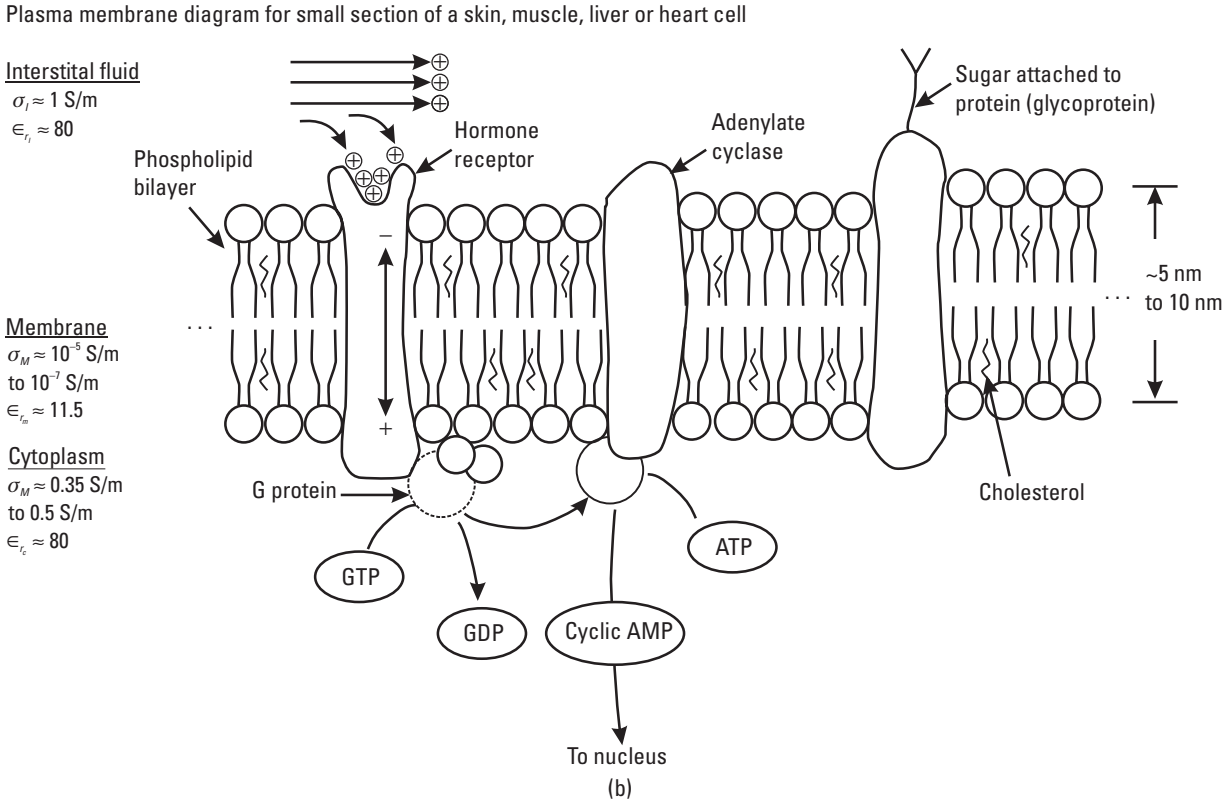


Figure 3.1 (continued.)

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

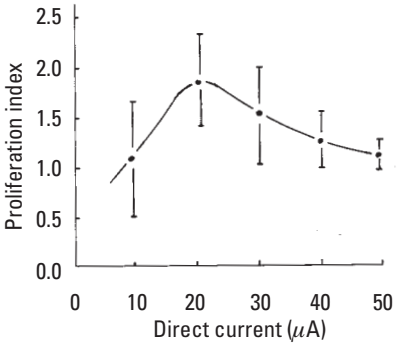
V/cm), very high direct current levels (approximately 2 mA), and exposure times of approximately 10 minutes or less, Viega et al. and Holandino et al. observed cell lysis, cell morphology variations, mitochondrial swelling, reductions in cell viability, and intense vacuolization in human leukemia K562 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.

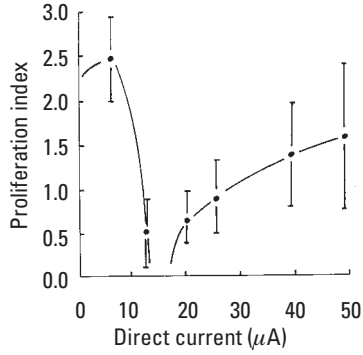
Lyte, Gannon, and O'Clock [21], O'Clock [22], and O'Clock and Leonard [23] reported a "window of suppression" for a number of different types of cancer cells (EL-4 lymphoma, IL-6 hybridoma, and retinoblastoma cells) at direct current levels that are much lower (less than 100 μA) and for much longer exposure 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.

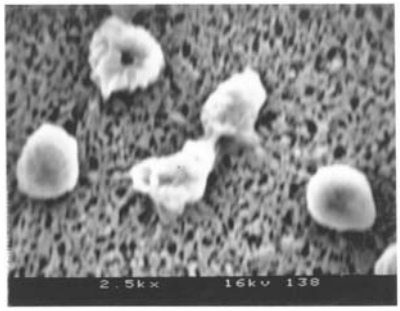


Proliferation index for normal retinal cells as a function of direct electrical current

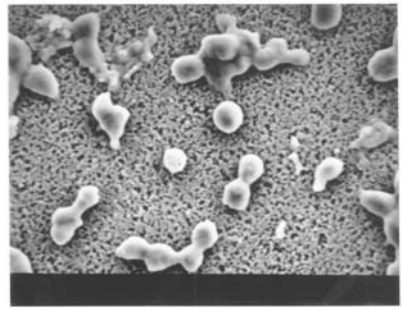


Proliferation index for malignant retinal (retinoblastoma) cells (approximately 750,000 cells/ml concentration) as a function of direct electrical current.

(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:

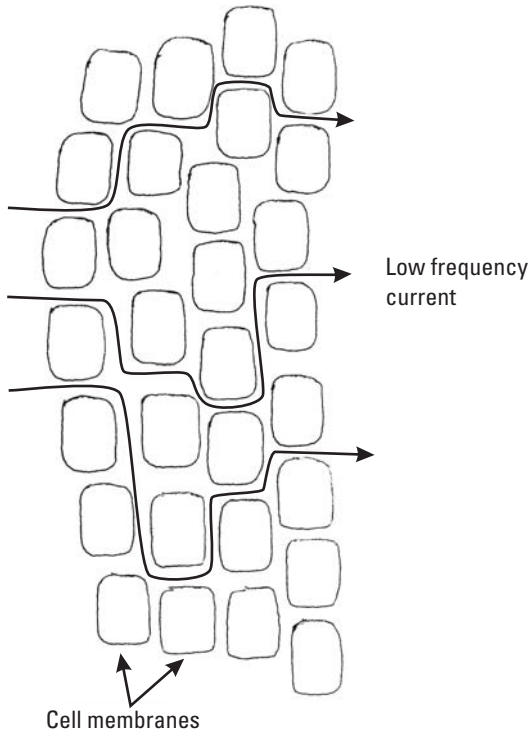


Figure 3.3 (a) Cells and interstitial spaces in tissue, meandering electrical current pathways for low-frequency currents, and electronic filter circuit analog. (b) Pathway for higher frequency electrical current through cells (displacement current). (c) Tissue impedance characteristics as a function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

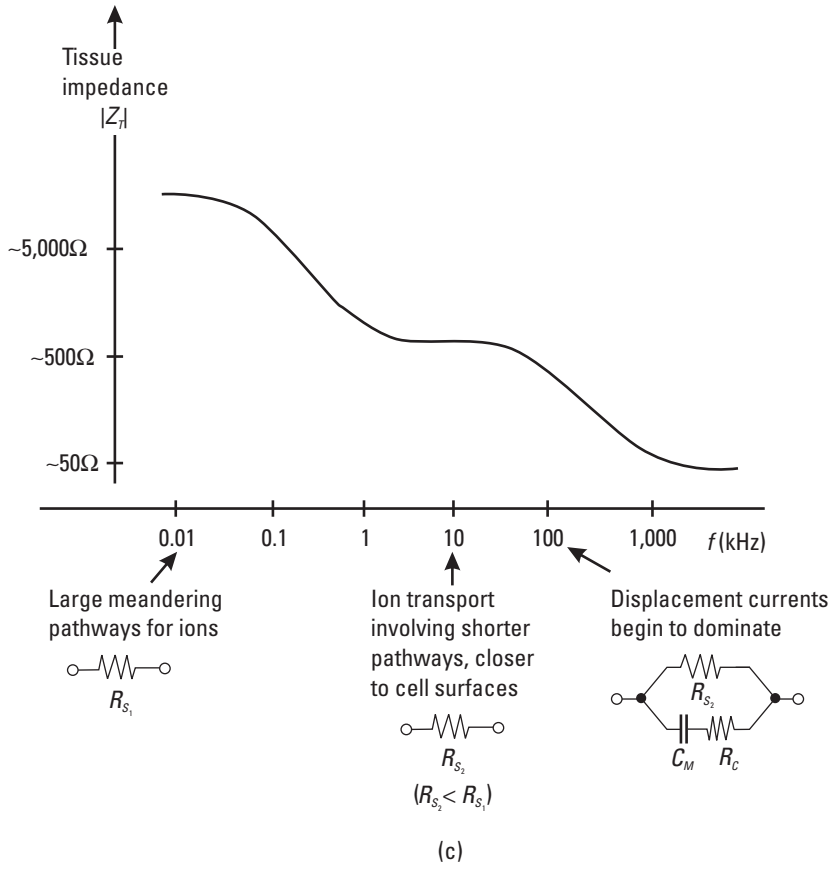


Figure 3.3 (continued.)

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

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.

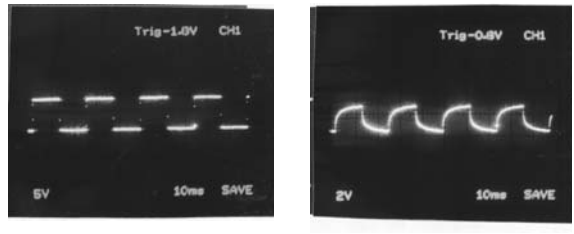
Bioelectric impedance analysis can yield useful diagnostic information on the condition and state of the body under diverse physiological or clinical circumstances [27]. A number of techniques have been proposed, using measurements of impedance and dielectric constant, to develop imaging techniques that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

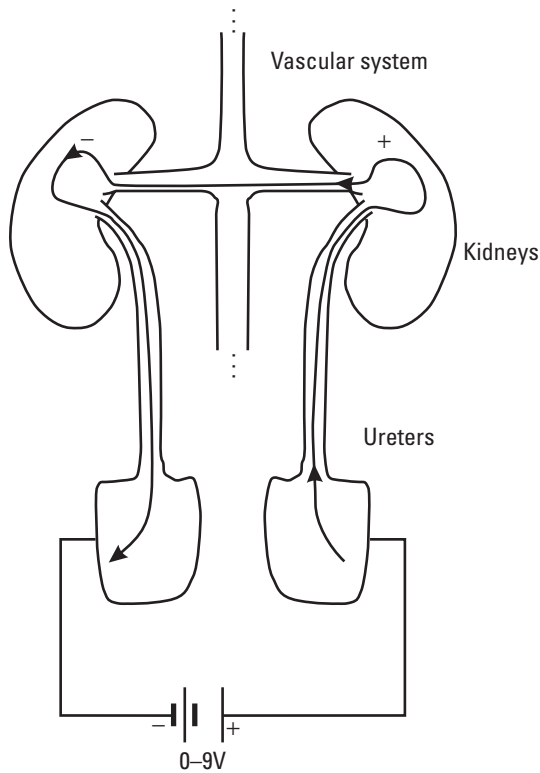


Figure 3.5 Experimental arrangement for evaluation of BCEC mechanisms in the renal system. Fluid excretion is enhanced by electro-osmotic flow of water toward the cathodic (negative electrode) kidney region.

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

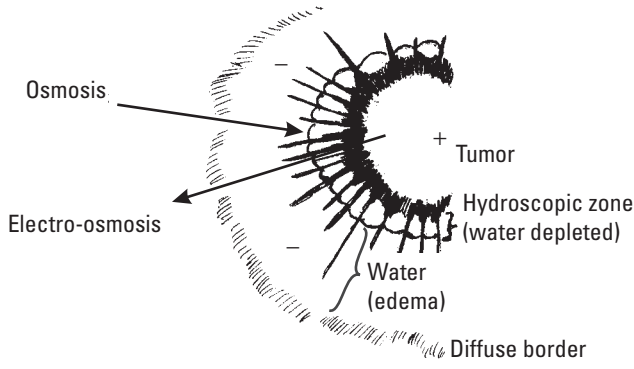


Figure 3.6 Drawing of a lung tumor necrosis with streaks, spikes, and corona structures in X-ray images as described by Nordenström.

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

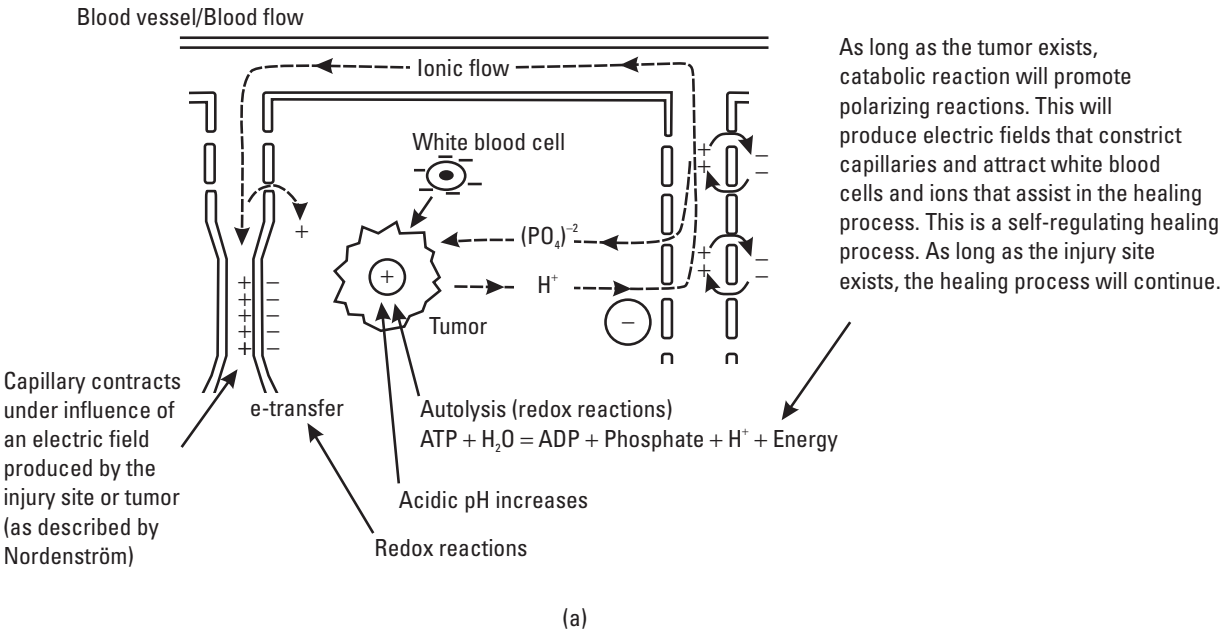


Figure 3.7 (a) A BCEC for the electropositive state of a tumor. In addition, water (not shown) is flowing into the tumor by osmosis and out of the tumor by electro-osmosis. (b) The electronegative state of a tumor. In this state, the transport of the fast moving, relatively light hydrogen molecules leaves 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.

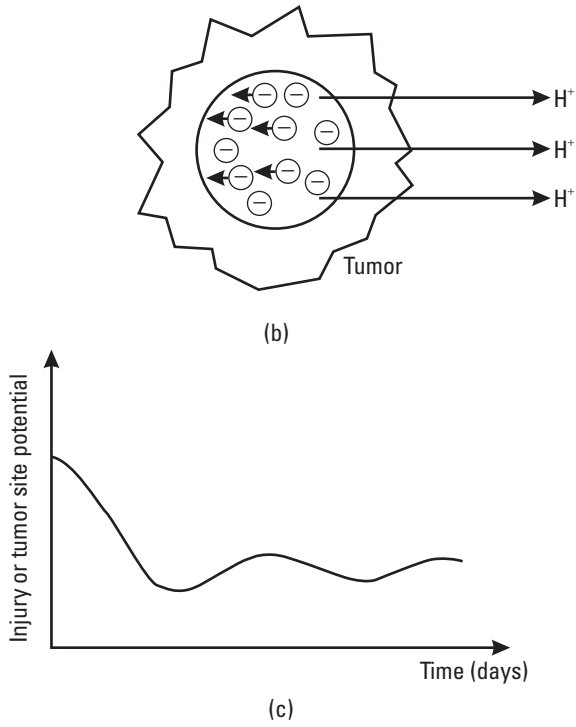


Figure 3.7 (continued.)

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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