Bioelectromagnetic Medicine

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Preface

A BRIEF HISTORICAL PERSPECTIVE

According to *The Yellow Emperor's Canon of Internal Medicine,* our oldest extant medical text, magnetic stones (lodestones) applied to acupuncture points were used to relieve pain and other complaints 40 centuries ago. The *Vedas,* religious scriptures of the Hindus also believed to be several thousand years old, similarly allude to the therapeutic powers of *ashmana* and *siktavati* (instruments of stone). The Greeks referred to these as *lapus-vivas* (live-stones) and Hippocrates purportedly used them to cure sterility. Egyptian physicians ascribed a variety of benefits to magnetic stones, as did early Buddhists. Tibetan monks still place bar magnets on the skull to improve the concentration and learning ability of novitiates in accordance with an age-old protocol.

In the early 1500s, the Swiss physician and alchemist Paracelsus became convinced that magnetism could restore the body's vitality and used magnets to promote healing and treat epilepsy, diarrhea, and certain types of hemorrhage. Lodestones were ground up to make powders that could be applied as magnetic salves or ingested to provide energy and stop bleeding. Such practices became very popular but were debunked in 1600 by William Gilbert in *De Magnete*. By the middle 1700s, more powerful, carbon-steel magnets had become available in Europe and there was heightened interest in their curative powers. Franz Anton Mesmer quickly became famous for his miraculous cures of everything from deafness to paralysis. In his 1775 report *On the Medicinal Uses of the Magnet,* he vividly described how he had restored health to a patient with uncontrollable seizures and numerous other nervous system complaints by feeding her iron filings and applying specially shaped magnets over affected organs. He later claimed that the healing force actually resided in his own "animal magnetism" *(magnetisomum animalem)*. This was hailed as a new force analogous to Newton's gravity, and people from all over Europe waited in long lines to be treated in his Paris salon. French physicians considered him a fraud and convinced Louis XVI to establish an unbiased commission consisting of Benjamin Franklin, Antoine Lavoisier, and Dr. J.I.Guillotin to investigate Mesmer's claims. They observed blindfolded patients who were exposed to very strong magnets and asked to describe their responses when fake objects were unknowingly substituted. The commission concluded in 1784 that magnetic healing was entirely due to the belief of the patient (placebo effect) and the power of suggestion (hypnosis). We still refer to hypnotism as "mesmerism."

Although Mesmer was thoroughly discredited, magnet therapy flourished in the United States and permanent magnet sales soared after the Civil War, particularly in the newly industrialized Western farm belts. Magnets, magnetic salves, and liniments were dispensed by traveling magnetic healers and were readily available at food and grain stores. By the turn of the century, mail-order catalogs offered magnetic soles for boots (profitable at 18 cents a pair) as well as magnetic rings, belts, caps, girdles, and other apparel

that purportedly could cure anything from menstrual cramps to baldness and impotence. The king of magnetic healers was Dr. C.J.Thacher, whose Chicago's Magnetic Company in the 1920s promised "health without the use of medicine." His mail-order pamphlet explained that the energy responsible for life comes from the magnetic force of the sun, which is conducted through the rich iron content of the blood. Disease resulted when stressful lifestyles and environmental factors interfered with these healing forces. However, "magnetism properly applied will cure every curable disease no matter what the cause." The most efficient way to expedite this alleged ability of iron in the blood to transmit healing magnetic energy was to wear magnetic clothing, and almost every conceivable garment was available. A complete costume, which promised "full and complete protection of all the vital organs of the body," contained 700 magnets!

It is not clear when electricity was first used to treat illness but electric catfish native to the Nile are portrayed in Egyptian murals several thousand years old that suggest medical applications. The Roman physician Scribonius Largus used a live torpedo fish to treat a patient with gout and wrote in 46 A.D. that headaches and other pains could be cured by standing in shallow water near these electric fish. The powerful South American electric eel was introduced to Europe in 1750, and people flocked to be treated with its "natural electricity." Around the same time, the invention of the Leyden jar had dramatically demonstrated the ability of a stored electrical charge to produce muscle contractions and shocks. The publication of Mary Shelley's *Frankenstein* in 1818 stimulated interest in electricity as the source of life. Since Galvani had shown that limbs or other body parts would jump when electrical shocks were administered to animal and human cadavers, it was believed that electricity could bring the dead to life. Various "reanimation" chairs and devices were constructed, some of which may possibly have acted as pacemakers or defibrillators in the rare cases that responded. An induction coil with sponge-tipped electrodes was used in 1853 to successfully treat abnormal heart rhythms and angina. Over the next few decades, as batteries were progressively improved and electricity from generating stations became available, all sorts of "medical coils" were developed with diverse curative claims.

By the early 1900s, electrotherapeutics was viewed as a legitimate medical specialty much like the growing fields of radiology and radium therapy, and medical textbooks devoted chapters to the use of magnetism and electricity. Devices were devised to diagnose and treat anemia, hysteria, convulsions, insomnia, migraine, neuralgia, arthritis, fatigue, and all types of pain. Some were based on the proposition that each organ or individual was "tuned" to a specific electromagnetic wavelength whose application could energize or rejuvenate them. The most popular were the dynamiser and oscilloclast devised by Albert Abrams, a physician who was described by the American Medical Association in 1925 as the "dean of twentieth century charlatans." The dyanimizer was said to be so sensitive it could not only diagnose a disease from a drop of blood, photograph, or handwriting sample but also pinpoint its location in the body. The oscilloclast was then simply set to the vibratory rate of the disease to be treated and the treatment was likened to shattering a wineglass with sound vibrations. A decade later, Wilhelm Reich claimed he had discovered a universal cosmic and biological energy called orgone that permeated the universe. He constructed an orgone accumulator box he claimed could collect and accumulate orgone obtained from the atmosphere. Sitting in the accumulator would not only restore and promote health and vitality but was an effective treatment for cancer. The FDA sued and convicted him for fraud, and the court ordered his books and research burned and his equipment destroyed. Although Abrams died in prison in 1957, he still has fervent followers who believe in his theories and devices, judging from various Web sites. Other contraptions made similar extravagant but worthless claims, so it is not surprising that all bioelectromagnetic approaches came to be regarded as fraudulent. A more detailed discussion of the above is available elsewhere (1).

Unfortunately, this dismissed included legitimate research, and it is not unlikely that in some instances the baby was thrown out with the bathwater. One example may be the work of Harold Saxton Burr, whose theory of "L fields" of life showed great potential for the diagnosis of cancer and the treatment of various disorders. His research results using the comparatively crude devices available over a half century ago are now being intensively reinvestigated and confirmed with more sophisticated technology. In recent years, magnetic resonance imaging (MRI) and positive emission tomography (PET scanning) have emerged as superior diagnostic aids. Cardiac pacemakers, defibrillators, and other implantable electromedical devices have saved countless lives and eased the suffering of patients with Parkinson's disease and other debilitating disorders. The FDA has also approved specific electromagnetic devices to promote the healing of bone fractures that have failed to unite despite other interventions; this procedure has proven successful and safe in hundreds of thousands of patients over the past few decades. More recently, electromagnetic therapies for the treatment of urinary incontinence, sports injuries, and liver and kidney tumors have also been approved. Other approaches, for the treatment of osteoarthritis, pain, tinnitus, and other indications, have satisfied criteria for efficacy and safety that have led to their approval in European and other countries and that may allow them to be available in the United States under the "globalization" and "harmonization" provisions of the 1997 FDA Modernization Act.

WHY AND HOW THIS BOOK WAS WRITTEN

Permanent magnet and electromagnetic therapies are now riding the crest of a tidal wave of interest in "alternative" and "complementary" medicine. Unfortunately, charlatans, entrepreneurs, and misguided zealots with worthless devices and unfounded claims still abound. It is essential to distinguish these from authentic approaches and products. As a result, in this book we have tried to separate the wheat from the chaff by restricting contributions to evidence-based medicine supported by references in peer-reviewed publications and to provide the reader with tools and skills for evaluating the legitimacy of devices and claims. In addition to a lengthy history of quackery and fraud, another criticism that has hampered wider acceptance of bioelectromagnetic approaches is the inability to identify the mechanisms of action responsible for any benefits. We have therefore attempted to identify concepts and theories that attempt to explain the mechanisms responsible for mediating the diverse benefits of bioelectromagnetic therapies and, in some instances, how they may relate to ancient concepts of subtle energies in the body that are also found in nature. How weak environmental electromagnetic energies as well as those generated internally can produce nonthermal biological effects is not clear since the absence of detectable heat exchange would appear to violate the laws of thermodynamics.

In addition, our current concept of how communication takes place in the body is at a chemical/molecular level as we visualize small peptide and other messengers fitting into specific receptor sites on cell walls much like keys opening certain locks. Such physical structural matching that could occur only on a random-collision basis cannot explain the myriad instantaneous and automatic reactions such as those that occur in "fight or flight" responses to severe stress. As will be seen, there is an emerging paradigm of cellular communication at a physical/atomic level that may provide some answers and also provide insights into widely acknowledged but poorly understood phenomena such as the placebo effect, the power of prayer and a firm faith, telepathic communication, the benefits of acupuncture, homeopathy, therapeutic touch, various bodywork and massage therapies, and Kirlian and other low-level imaging procedures.

Another issue that has caused wariness about bioelectromagnetic therapies are safety concerns about possible increased risk of certain malignancies and birth defects resulting from proximity to high power lines, cell phones, microwave ovens, and electric blankets. It is not surprising that electromagnetic fields,

like many other therapies, can be two-edged swords. For example, all the modalities we use to treat cancer, including radiation, chemotherapy, and hormonal interventions, can also cause cancer. Such effects may depend on dosage, duration of exposure, and genetic and other influences. It is not likely that any clear conclusion about adverse electromagnetic effects can be reached until more information has been obtained from long-term studies that focus on these factors. For this reason, we have refrained from participating in this debate other than to devote a chapter on the importance of dosimetry and to emphasize that no such adverse effects have been observed or seem likely in the therapies presented in this book. Indeed, those that have been proposed and implemented by Demetrio Sodi Pallares and Björn Nordenström and confirmed by others have shown stunning success in treating various malignancies. Many of the chapters in this book are based on presentations at the annual International Congress on Stress over the past decade or so, and additional information on these events can be obtained at www.stress.org.

We have also attempted in this book to trace the origin and development of various therapies, such as TENS and vagal nerve stimulation by pioneers in the field such as Norman Shealy, Donlin Long, and Jacob Zabara. Kirk Jeffrey has contributed a similar chapter on the evolution of cardiac pacemakers. We have made a concerted effort to include prominent scientists whose research may not be well known in the United States. When initially approached to serve as editor of this book, I explained that this was not my field of expertise and asked Marko Markov, a distinguished physicist, to serve as coeditor. He is also much more familiar with relevant advances in Eastern Europe and Russia, and I am grateful for his careful review of all chapters and for those he has attracted from these countries as well as his own contributions. I am also indebted to Russell Dekker for expediting this work so that the material would be current and important late-breaking advances could be included, such as radiofrequency coblation nucleoplasty for disc disease. I would also like to thank all the authors for their cooperation in responding so promptly to urgent requests for revisions necessary to adhere to this very accelerated publication schedule.

The above is a brief summary of why this book is needed and how it was assembled. I believe it is particularly appropriate to conclude with the following quotation.

> In the decade to come, it is safe to predict, bioelectromagnetics will assume a therapeutic importance equal to, or greater than, that of pharmacology and surgery today. With proper interdisciplinary effort, significant inroads can be made in controlling the ravages of cancer, some forms of heart disease, arthritis, hormonal disorders, and neurological scourges such as Alzheimer's disease, spinal cord injury, and multiple sclerosis. This prediction is not pie-in-the-sky. Pilot studies and biological mechanisms already described in primordial terms, form a rational basis for such a statement. — *J.Andrew L.Bassett, 1992*

Andy Bassett was one of the early advocates of the use of electromagnetic fields for uniting fractures that refused to heal. Unfortunately, he died before he could see that his prophecy would come true well ahead of schedule. In many respects, this book is a tribute to him and other pioneers such as Bob Becker, Abe Liboff, Björn Nordenström, and Ross Adey who recognized the vast potential of bioelectromagnetic medicine and have helped to put it on a solid scientific footing. I am particularly delighted that we were able to obtain contributions from most of these trailblazers.

Paul J.Rosch, M.D., F.A.C.P.

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Bioelectromagnetic Medicine

1
Potential Therapeutic Applications of Nonthermal Electromagnetic Fields: Ensemble Organization of Cells in Tissue as a Factor in Biological Field Sensing*

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There are major unanswered questions about possible health risks that may arise from human exposures to various man-made electromagnetic fields where these exposures are intermittent, recurrent, and may extend over a significant portion of the lifetime of the individual. Current equilibrium thermodynamic models fail to explain an impressive spectrum of observed electromagnetic bioeffects at nonthermal exposure levels. Much of this signaling within and between cells may be mediated by free radicals of the oxygen and nitrogen species.

I.
INTRODUCTION

In our solar system, the natural electromagnetic environment varies greatly from planet to planet. In the case of the planet Earth, a semiliquid ferromagnetic core generates a major and slowly migrating *static* geomagnetic field. Concurrently, there are much weaker natural *oscillating* low-frequency electromagnetic fields that arise from two major sources: in thunderstorm activity in equatorial zones of Central Africa and the Amazon basin and in lesser degree from solar magnetic storms in years of high activity in the 11-year solar sunspot cycle.

A.
Comparison of Natural and Man-Made Electromagnetic Environments

All life on earth has evolved in these fields. Defining them in physical terms permits direct comparison with far stronger man-made fields that have come to dominate all civilized environments in the past century. Energy in the *oscillating* natural fields is almost entirely in the extremely low frequency (ELF) spectrum, with peaks at frequencies between 8 and 32 Hz, the Schumann resonances (1). Their electric components are around 0.01 V/m, with magnetic fields of 1–10 nT. These natural oscillations are ducted worldwide between the earth's surface and the ionosphere at an approximate height of 250 km. With a circumference of 41,000 km, the earth may act as a cavity resonator for this ducted propagation (at the velocity of light, 300,000 km/s), behaving resonantly at a frequency around 8Hz. Neither solar nor terrestrial sources contribute significant amounts of radiofrequency or microwave energy to the earth's biosphere, and we may

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contrast these weak ELF fields with the earth's much larger static geomagnetic field around 50 μT (0.5 gauss).

The earth's *static* magnetic field at 50 μT is 5000 times larger than the natural oscillations but still substantially less than a wide range of daily human exposures to static and oscillating fields in domestic and occupational environments.

Generation and distribution of electric power has spawned a vast and ever growing vista of new electronic devices and systems. They overwhelm the natural electromagnetic environment with more intense fields. They include oscillations far into the microwave spectrum, many octaves higher than the Schumann resonances. This growth of radio-frequency (RF) and/or microwave fields is further complicated by the advent of digital communication techniques. In many applications, these microwave fields, oscillating billions of times per second, are systematically interrupted (pulsed) at low frequencies. This has raised important biological and biomedical questions, still incompletely answered, about possible tissue mechanisms in detection of amplitude- and pulse-modulation of RF and/or microwave fields (2).

B. Historical Evidence on Possible Health Effects of Man-Made Environmental Fields

There are major unanswered questions about possible health risks that may arise from human exposures to various man-made electromagnetic fields where these exposures are intermittent, recurrent, and may extend over a significant portion of the lifetime of the individual. Historical correlations have been reported between growth of rural electrification in the United States and the United Kingdom and an increased incidence of childhood leukemia. A peak in childhood leukemia at ages 2 through 4 emerged de novo in the 1920s. Using U.S. census data for 1930, 1940, and 1950, Milham and Osslander (3) concluded that the peak in the common childhood acute lymphoblastic leukemia (ALL) may be attributable to electrification.

Design of modern office buildings has led to their electrification through one or more large distribution transformers that may be located in basement vaults, or in some cases, located on each floor of the building. Milham (4) has examined cancer incidence in such a building over a 15-year period and found evidence for *cumulative risks*. An analysis of linear trend in cancer incidence, using average years employed as an exposure score, was positive (P=0.00337), with an odds ratio of 15.1 in workers employed longer than 5 years.

In large modern offices, the electromagnetic environment has been further complicated by introduction of local area networks (LANs) for local telephonic (voice) and data transmission. Workers may be continuously exposed to fields from a plethora of sources located on each computer and on local network controllers. Their power output is typically in the low milliwatt to microwatt range—so low that significant heating of workers' tissues is improbable. Any bioeffects attributable to their operation strongly suggest *nonthermal* mech anisms of interaction, and raise further important questions about mechanisms mediating a cumulative dose from repeated, intermittent exposures, possibly over months and years. None of these studies support tissue heating as an adequate model for bioeffects seen in a wide spectrum of laboratory experiments (see below) or in reported epidemiological findings.

The American National Standards Institute (1992) first recognized a tissue dose of 4.0 W/kg as a *thermal* (heating) tissue threshold possibly associated with adverse health effects and proposed an exposure limit in controlled environments (occupational) at 0.4 W/kg, thus creating a supposed "safety margin" of 10. For uncontrolled environments (civilian), a larger safety margin was set with a permissible exposure limit (PEL) 50 times lower at 0.08 W/kg. Since actual measurement of tissue SARs under environmental conditions is

not a practical technique, PELs are typically expressed as a function of *incident field power density,* the amount of energy falling on a surface per unit area, and expressed in mW/cm^2.

More recently, the U.S. government Interagency Radio Frequency Working Group (1999) has emphasized the need for revisions recognizing nonthermal tissue microwave sensitivities:

> Studies continue to be published describing biological responses to nonthermal ELF-modulated RF radiation exposures that are not produced by CW (unmodulated) radiation. These studies have resulted in concern that exposure guidelines based on thermal effects, and using information and concepts (time-averaged dosimetry, uncertainty factors) that mask any differences between intensity-modulated RF radiation exposure and CW exposure, do not directly address public exposures, and therefore may not adequately protect the public.

II. INITIAL TRANSDUCTION OF IMPOSED MICROWAVE FIELDS AT NONTHERMAL ENERGY LEVELS *t*

Tissue components of environmental RF and microwave fields are consistent with two basic models. Sources close to the body surface produce *near-field exposures,* as with users of mobile phones. The emitted field is magnetically coupled directly from the antenna into the tissues. At increasing distances from the source, the human body progressively takes on properties of a radio antenna, with absorption of radiated energy determined by physical dimensions of the trunk and limbs. This is a *far-field exposure,* defined as fully developed at 10 or more wavelengths from the source and based on interactions with the electric component of the radiated field. Permissible exposure limits (PELs) have rested on measurement of microwave field energy absorbed as heat, expressed as the *specific absorption rate (SAR)* in W/kg.

There is an initial dichotomy in possible modes of interaction of cells in tissue with environmental microwave fields. It is principally determined by the separation of responses attributed to tissue heating from those elicited by certain fields at levels where frank heating is not the basis of an observed interaction. Their interpretation and possible significance has required caution in both biological and biophysical perspectives. Many of these biological sensitivities run counter to accepted models of physiological thresholds based in equilibrium thermodynamics of kT thermal collision energies. In a physical perspective, the search also continues for biological systems compatible with a first transductive step in a range of functionally effective vibrational and electromagnetic stimuli that are orders of magnitude weaker than kT. Aspects of these findings are reviewed in (Sec. IV.) Their occurrence invites hypotheses on directions of future research (5).

A. Cell Membranes as the Site of Initial Field Transductive Coupling

Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both ELF and microwave fields for many neurotransmitters (6), hormones (7, 8), growth-regulating enzyme expression (9–12), and cancer-promoting chemicals (13). In none of these studies does tissue heating appear involved causally in the responses (2). Physicists and engineers have continued to offer microthermal, rather than athermal, models for these phenomena (14, 15) with views that exclude consideration of cooperative organization and coherent charge states, but it is difficult to reconcile experimental evidence for

factors such as modulation frequency dependence and required duration of an amplitude-modulated signal to elicit a response *(coherence time)* (11) with models based on the equilibrium dynamics of tissue heating.

B. Evidence for Role of Free Radicals in Electromagnetic Field Bioeffects

Examination of vibration modes in biomolecules, or portions of these molecules (16) has suggested that resonant microwave interactions with these molecules, or with portions of their structure, is unlikely at frequencies below higher gigahertz spectral regions. This has been confirmed in studies showing collision-broadened spectra, typical of a heating stimulus, as the first discernible response of many of these molecules in aqueous solutions to microwave exposures at frequencies below 10 GHz.

However, there is an important option for biomolecular interactions with static and oscillating magnetic fields through the medium of *free radicals* (see Refs. 17 and 18 for summaries). Chemical bonds are magnetic bonds, formed between adjacent atoms through paired electrons having opposite spins and thus magnetically attracted. Breaking of chemical bonds is an essential step in virtually all chemical reactions, each atomic partner reclaiming its electron, and moving away as a free radical to seek another partner with an opposite electron spin. The brief lifetime of a free radical is about a nanosecond or less, before once again forming a *singlet pair* with a partner having an opposite spin or for electrons with similar spins, having options to unite in three ways, forming *triplet pairs* (reviewed in Ref. 2).

During this brief lifetime, imposed magnetic fields may delay the return to the singlet pair condition, thus influencing the *rate* and the *amount of product* of an ongoing chemical reaction (19). McLauchlan points out that this model predicts a potentially enormous effect on chemical reactions for static fields in the low mT range. For oscillating fields, the evidence is less clear on their possible role as direct mediators in detection of ELF frequency-dependent bioeffects. *Spin-mixing* of orbital electrons and nuclear spins in adjacent nuclei is a possible mechanism for biosensitivities at extremely low magnetic field levels, but these interactions are multiple, complex, and incompletely understood (20). The highest level of free radical sensitivity may reside in hyperfine-dependent singlet-triplet state mixing in radical pairs with a small number of hyperfine states that describe their coupling to nearby nuclei (21, 22). Although sensitivities to magnetic fields in such a system might theoretically extend down to zero magnetic field levels, singlet-triplet interconversion would need to be sufficiently fast to occur before diffusion reduced the probability of radical re-encounter to negligible levels.

Lander (23) has emphasized that we are at an early stage of understanding free radical signal transduction. "Future work may place free radical signaling beside classical intra- and intercellular messengers and uncover a woven fabric of communication that has evolved to yield exquisite specificity." A broadening perspective on actions of free radicals in all living systems emphasizes a dual role: first, as messengers and mediators in many key processes that regulate cell functions throughout life and second, in the pathophysiology of *oxidative stress diseases*.

At cell membranes, free radicals may play an essential role in regulation of receptor specificity, but not necessarily through a lock-and-key mechanism. As an example, Lander cites the location of cysteine molecules on the surface of P21-*ras* proteins at cell membranes. They may act as selective targets for nitrogen and oxygen free radicals, thereby inducing covalent modifications and thus setting the *redox potential* of this target protein molecule as the critical determinant for its highly specific interactions with antibodies, hormones, etc. Magnetochemistry studies have suggested a form of cooperative behavior in populations of free radicals that remain *spin-correlated* after initial separation of a singlet pair (24). Magnetic fields at 1 and 60 Hz destabilize rhythmic oscillations in brain hippocampal slices at 56 μT (0.35

to 3.5 nV mm^{-1}) via as yet unidentified nitric oxide mechanisms involving free radicals (23, 25). In a general biological context, these are some of the unanswered questions that limit free radical models as general descriptors of threshold events.

III.
SENSITIVITIES TO NONTHERMAL STIMULI: TISSUE STRUCTURAL AND FUNCTIONAL IMPLICATIONS

A.
Conductance Pathways in Multicellular Tissues

In its earliest forms, life on earth may have existed in the absence of cells, simply as a "soup" of unconstrained biomolecules at the surface of primitive oceans. It is a reasonable assumption that the first living organisms existed as single cells floating or swimming in these primordial seas. Concepts of a cell emphasize the role of a bounding membrane, surrounding an organized interior that participates in the chemistry of processes essential for all terrestrial life. This enclosing membrane is the organism's window on the world around it.

For unicellular organisms that swim through large fluid volumes, the cell membrane is both a sensor and an effector. As a sensor, it detects altered chemistry in the surrounding fluid and provides a pathway for inward signals generated on its surface by a wide variety of stimulating ions and molecules, including hormones, antibodies, and neurotransmitters. These most elemental inward signals are susceptible to manipulation by a wide variety of natural or imposed electromagnetic fields that may also pervade the pericellular field. As effectors, cell membranes may also transmit a variety of electrical and chemical signals across intervening intercellular fluid to neighboring cells, thus creating a domain or ensemble of cells, often able to "whisper together" in a faint and private language. Experimental evidence suggests that these outward effector signals may also be sensitive to intrinsic and imposed electromagnetic fields.

Rather than being separated in a virtually limitless ocean, cellular aggregates that form tissues of higher animals are separated by narrow fluid channels that take on special importance in signalling from cell to cell. Biomolecules travel in these tiny "gutters," typically not more than 150 Å wide, to reach binding sites on cell membrane receptors. These gutters form the *intercellular space* (ICS). It is a preferred pathway for induced currents of intrinsic and environmental electromagnetic fields. Although it occupies only ~10% of the tissue cross section, it carries at least 90% of any imposed or intrinsic current, directing it along cell membrane surfaces. Whereas the ICS may have a typical impedance of ~4–50 ohm cm^{-1}, transmembrane impedances are ~10^4–10^6 ohm cm^{-2}.

B.
Structural and Functional Organization of the Extracellular Space

The organization of cell membrane surfaces and intercellular gutters in detection of these tissue components of extrinsic and intrinsic electromagnetic fields enters the realm of *nonequilibrium* thermodynamics (26, 27), characterized by *cooperative processes,* mediated by *coherent states* of electric charges on cell membrane surface molecular systems.

Spaces in the ICS are not simple saline filled channels. Numerous stranded protein molecules protrude into these spaces from the cell interior and form a *glycocalyx* with specialized receptor sites that sense chemical and electrical stimuli in surrounding fluid. Their amino sugar tips are highly negatively charged

(polyanionic) and attract a *polycationic* atmosphere, principally of calcium and hydrogen ions. This Debye layer has an extremely high virtual dielectric constant at low frequencies (D_k>10^6 at frequencies<1 kHz) (28). Biological cooperative processes occur in systems where at least one energetic parameter in that system (e.g., temperature, electric charge) has been moved far from equilibrium by the addition of external energy. This added energy may induce a population of substrate elements, all at the same higher energy level—a *coherent* energetic state. In such a system, a weak external trigger may elicit a *cooperative* process, with an energy release far greater than in the initial trigger. Capping and patching on the lymphocyte cell surface (29) offers a striking example of such a cooperative response, based on intracellular metabolic energy.

The proteins of the glycocalyx offer an anatomical substrate for the first detection of weak electrochemical oscillations in pericellular fluid, including field potentials arising in activity of adjoining cells, or as tissue components of environmental fields. Research in molecular biology has increasingly emphasized essentially direct communication between cells due to their mutual proximity. Bands of *connexin* proteins form *gap junctions* directly uniting adjoining cell membranes. Experimental evidence supports their role in intercellular signaling.

C.
Tissue Detection of Low Frequency Fields and RF/Microwave Fields Amplitude-Modulated at Low Frequencies: Structural and Functional Options

Differential bioeffects, to be discussed below, have been reported between certain nonthermal RF or microwave fields with low-frequency amplitude or pulse modulation when compared to exposures to unmodulated continuous wave (CW) fields at similar power levels. The findings suggest, but do not yet establish unequivocally, that this frequency dependence may be a system property in a sequence of molecular hierarchies beyond the first transductive step. If the concept of modulation frequency-dependence continues to gain support in further research, answers must be sought as to the manner of its detection.

For ELF fields, models based on joint static-oscillating magnetic fields have been hypothesized. They include ion cyclotron resonance (30), where mono- and divalent cations, such as potassium and calcium (abundant in the cellular environment), may exhibit cyclotron resonance at ELF frequencies in the presence of ambient static fields of less than 100 μT, such as the geomagnetic field. Other models describing ELF frequency dependence have considered phase transitions (31) and ion parametric resonance (32), but interpretation of this frequency dependence based on ion parametric resonance remains unclear (33).

For amplitude- or pulse-modulated RF and/or microwave fields, there is the implication that some form of *envelope demodulation* occurs in tissue recognition of ELF modulation components, but the tissue may remain essentially transparent to the same signal presented as an unmodulated carrier wave (2, –34). However, crucial questions remain unanswered. It is not known whether biological low-frequency dependence is established at the transductive step in the first tissue detection of the field, or whether it resides at some higher level in an hierarchical sequence of signal coupling to the biological detection system (35). For ELF magnetic fields, experimental evidence points to a slow time scale in inhibition of tamoxifen's antiproliferative action in human breast cancer cells (36).

It is a principle of radio physics that extraction of ELF modulation information from an amplitude-modulated signal requires a *nonlinear element* in the detection system. This required nonlinearity may involve a spatial component, such as differential conduction in certain directions along the signal path, or the path itself may exhibit nonlinearities with respect to such factors as spatial distribution of electric

charges at fixed molecular sites (so-called fixed charges), or conduction itself may involve a nonlinear quantum process, as in electron tunneling across the transverse dimensions of the cell membrane.

These constraints impose a further essential condition for demodulation to occur in the multicellular tissues of living organisms. There must be a *site for demodulation* to occur. Evidence supports a role for cell membranes to act in this way, based not only on their intrinsic structure, but also on their proximity to neighboring cells in the typical organization of tissues of the body. Typical tissue organization meets the three criteria outlined above but as a cautionary note, does not allow calculation of possible detection efficiency. Direct neighbor-neighbor cellular interactions will invite our further consideration of properties of cellular ensembles or domains in determining tissue threshold sensitivities.

1. Directional Differences in Tissue Signal Paths

As already noted, the narrow gutters of the intercellular spaces offer preferred conduction pathways, with conductivity 10^2–10^4 higher through extracellular spaces than through cell membranes (37). Thus, the intercellular spaces become preferred pathways for *conduction along (parallel to) cell membrane surfaces* and will reflect the changing directions and cross sections of a myriad channels. Although predominantly an ionic (resistive) conduction pathway, it may also exhibit reactive components, due to the presence of protein molecules in solution.

2. Nonlinearities in Extracellular Spaces Related to Electric Charge Distribution

A suggested basis for envelope demodulation at cell surfaces may reside in the intensely anionic charge distribution on strands of glycoprotein that protrude from the cell interior, forming the glycocalyx (2, 38). As already noted, they provide the structural basis for specific receptor sites, and they attract a surrounding cationic atmosphere composed largely of calcium and hydrogen ions. This charge separation creates a Debye layer. In models and experimental data from resin particles, Einolf and Carstensen (28) concluded that this physical separation creates a large virtual surface capacitance, with dielectric constants as high as 10^6 at frequencies below 1 kHz. Displacement currents induced in this region by ELF modulation of an RF field may then result in demodulation.

3. Electron Tunneling in Transmembrane Conduction: Nonlinearities in Space and Time

Experimental studies of transmembrane charge tunneling by DeVault and Chance (39) and their more recent theoretical development by Moser et al. (40) offer an example of extreme functional nonlinearity within the cell membrane. Chance described temperature-independent millisecond electron transfer over a temperature range from 120K to 4K. Considering a cell membrane transverse dimension of 40 Å, Moser et al. noted that a variation of 20 Å in the distance between donors and acceptors in a protein changes the electron transfer rate by 10^{12}-fold. Concurrently in the time domain, the electron transfer rate is pushed from seconds to days, or a 10-fold change in rate for a 1.7 Å change in distance.

4. Issues of Comparability Between Bioeffects of ELF Fields, ELF-Modulated RF Fields, and Unmodulated (CW) RF Fields

From the beginning of these studies in the 1970s, it was noted that there were similarities in responses of tissues and cultured cells to environmental fields that were either in the ELF spectrum or were RF and/or microwave fields modulated at ELF frequencies. Available evidence has indicated similarities between certain cell ionic and biochemical responses to ELF fields and to RF and/or microwave fields amplitude modulated at these same ELF frequencies, suggesting that tissue demodulation of RF and/or microwave fields may be a critical determinant in ensuing biological responses.

These findings have been reviewed in detail elsewhere (2, 18). They are briefly summarized here in experiments at progressively more complex levels in the hierarchies of cellular organization. Early studies described calcium efflux from brain tissue in response to ELF exposures (38, 41), and to ELF-modulated RF fields (38, 41–43). Calcium efflux from isolated brain subcellular particles (synaptosomes) with dimensions under 1.0 μm also exhibit an ELF modulation frequency dependence in calcium efflux, responding to 16-Hz sinusoidal modulation, but not to 50 Hz modulation, nor to an unmodulated RF carrier (44). In the same and different cell culture lines, the growth regulating and stress responsive enzyme ornithine decarboxylase (ODC) responds to ELF fields (11, 45) and to ELF-modulated RF fields (9, 11, 12).

In more recent studies also related to cellular stress responses, Goodman and Blank and their colleagues have reported rapid, transitory induction of heat shock proteins by microtesla-level 60-Hz magnetic fields (46). In human HL60 promyelocytic cells these exposures at normal growth temperatures activated heat shock factor 1 and heat shock element binding, a sequence of events that mediates stress-induced transcription of the stress gene HSP70 and increased synthesis of the stress response protein hsp70kd. Thus, the events mediating the field-stimulated response appeared similar to those reported for other physiological stressors (hyperthermia, heavy metals, oxidative stress), suggesting to the authors a general mechanism of electromagnetic field interaction with cells. Their further studies have identified endogenous levels of c-*myc* protein as a contributor to the induction of HSP70 in response to magnetic field stimulation (47), with the hypothesis that magnetic fields may interact directly with moving electrons in DNA (48–50).

Immune responses of lymphocytes targeted against human lymphoma tumor cells (allogeneic cytotoxicity) are sensitive to both ELF exposures (51) and to ELF-modulated fields, but not to unmodulated fields (52).

Communication between brain cells is mediated by a spectrum of chemical substances that both excite and inhibit transaction and transmission of information between them. Cerebral amino acid neurotransmitter mechanisms (glutamate, GABA and taurine) are influenced by ELF fields (25, 53), and also by ELF-modulated microwave fields, but not by unmodulated fields. Kolomytkin et al. (6) examined specific receptor binding of three neurotransmitters to rat brain synaptosomes exposed to either 880- or 915-MHz fields at maximum densities of 1.5 mW cm^{-2}. Binding to inhibitory gamma-aminobutyric acid (GABA) receptors decreased 30% at 16 pulses/s, but was not significantly altered at higher or lower pulse frequencies. Conversely, 16 pulses/s modulation significantly increased excitatory glutamate receptor binding. Binding to excitatory acetyl choline receptors increased 25% at 16 pulses/s, with similar trends at higher and lower frequencies. *Sensitivities* of GABA and glutamate receptors persisted at field densities as low as 50 μW cm^{-2}.

A selective absence of responses to unmodulated (CW) RF and/or microwave fields reported in many of these earlier studies has focused attention on establishment of threshold sensitivities to CW field exposures. De Pomerai et al. (54) have reported cellular stress responses in a nematode worm as a biosensor of prolonged CW microwave exposures at athermal levels. Tattersall et al. (55) exposed slices of rat

hippocampal cerebral tissue to 700-MHz CW fields for 5–15 min at extremely low SARs in the range 0.0016–0.0044 W kg^{-1}. No detectable temperature changes (+/−0.1°C) were noted during 15-min exposures. At low field intensities, a 20% potentiation of electrically evoked population potentials occurred, but higher field intensities evoked either increased or decreased responses. The exposures reduced or abolished chemically induced spontaneous epileptiform activity. Bawin et al. (25) also tested the rat hippocampal slice, using ELF magnetic fields. At 56 μT (0.35–3.5 nV mm^{-1}), magnetic fields destabilized rhythmic electrical oscillations via as yet unidentified nitric oxide mechanisms involving free radicals.

D. The Roles of Field Intermittency and Exposure Duration in Seeking Optimal Therapeutic Responses: Possible "Time Windows" in Trans-Membrane Signaling Paths

It has been apparent from the earliest clinical applications of pulsed magnetic fields to such problems as delayed fracture healing that continuous exposure is not an optimal technique. For example, initial tests with FDA-approved 76-Hz magnetic field generators and cultured bone samples or osteoblast cell lines revealed a range of hormonal and enzymatic responses that occurred only at the onset or immediately after termination of field exposures. In turn, similar clinical testing of various exposure schedules in bone healing led to adoption of intermittent exposure regimes (56). In B-lineage lymphoid cells exposed to 60-Hz magnetic fields, Uckun et al. (57) reported an initial stimulation of tyrosine protein kinases (PTKs) Lyn and Syk. Activation of these Src proto-oncogene PTKs is a proximal and mandatory step in the later activation of protein kinase C. They play "a myriad roles" in signal cascades affecting proliferation and survival of B lymphoid cells.

How does a cell distinguish between transient and sustained signaling? Murphy et al. (58) have shown that in 3T3 fibroblasts, the immediate early gene *c-Fos* functions as a sensor for duration of activation of *extracellular-signal-regulated kinases* (ERK-1 and ERK-2). When ERK activation is transient (30–45 min), its activity declines before the *c-Fos* protein accumulates, and under these conditions *c-Fos* is unstable. However, when ERK signaling is sustained beyond 60 min, *c-Fos* is phosphorylated by still active ERK and by RSK (90K-ribosomal S6 kinase), thus exposing a docking site for ERK (the DEF domain). Together, these data identify a time-dependent general mechanism by which cells can interpret differences in ERK activation kinetics, including control of cell cycle progression towards either differentiation or proliferation.

Rudiger et al. (59) have reported an optimal timing sequence of 5 min ON, 10 min OFF in induction of DNA single and double strand breaks in human diploid fibroblasts and blood lymphocytes. The response to 50-Hz sinusoidal magnetic fields was dose dependent with a threshold at 70 μT. Also using cultured fibroblasts, Litovitz et al. (11) determined the minimal duration that a single low-frequency modulation frequency must be sustained *(coherence time)* in order to elicit activity in the enzyme ornithine decarboxylase (ODC). Using a 915-MHz field, switching modulation frequencies from 55 to 65-Hz at coherence times of 1 s or less abolished enhancement of ODC responses, while coherence times of 10 s or longer produced full enhancement.

It is abundantly clear that such a patchwork of observations fails to provide a database that would allow selection of optimal temporal stimulus patterns in specific clinical situations. Nevertheless, they may be considered the first pointers to crucial stimulus parameters, essential in the foundations of all magnetotherapy. They emphasize the importance of further research in that direction to define both the physical characteristics of an optimal stimulus pattern, and more importantly, the cell and molecular biology in underlying tissue substrates.

IV.
THE ROLE OF CELLULAR ENSEMBLES IN SETTING TISSUE THRESHOLDS FOR INTRINSIC AND ENVIRONMENTAL STIMULI

Our pursuit of mechanisms mediating tissue electromagnetic sensitivities at nonthermal levels raises questions about the relevance of observed thresholds in the sensory physiology of other modalities. By extrapolation, do these data suggest the need to explore collective properties of populations of cells in setting thresholds by forms of intercellular communication? Do cooperative processes yield one or more faint and private languages that allow ensembles of cells to whisper together in one or more faint and private languages? Do observed tissue-sensory thresholds differ significantly from thresholds measured in single cells in isolation from their neighbors?

A.
Evidence for Domain Functions as a General Biological Property in Tissues

Research in sensory physiology supports this concept, i.e., that some threshold properties may reside in highly cooperative properties of populations of elements rather than in a single detector (60). Seminal observations in the human auditory system point to a receptor vibrational displacement of 10^{-11} m, or approximately the diameter of a single hydrogen atom (61, 62); human olfactory thresholds for musk occur at 10^{-13} M, with odorant molecules distributed over 240 mm^2 (63); and human detection of single photons of blue-green light occurs at energies of 2.5 eV (64). In another context, pathogenic bacteria, long thought to operate independently, exhibit ensemble properties by communication through a system recognizing colony numbers as an essential step preceding release of toxins. These *quorum sensing* systems may control expression of virulence factors in the lungs of patients with cystic fibrosis (65).

1.
Domain Properties in Systems of Excitable Cells

Bialek addressed the problem of the auditory receptor in quantum mechanical terms. He evaluated two distinct classes of quantum effects: a *macroquantum effect,* typified by the ability of the sensory system to detect signals near the quantum limits to measurement, and a *microquantum effect,* in which "the dynamics of individual biological macromolecules depart from predictions of a semiclassical theory." Bialek concluded that quantum-limited sensitivity occurs in several biological systems, including displacements of sensory hair cells of the inner ear. Remarkably, quantum limits to detection are reached in the ear in spite of seemingly insurmountable levels of thermal noise.

To reach this quantum limit, these receptor cells must possess amplifiers with noise performance approaching limits set by the uncertainty principle. It is equally impressive that suppression of intrinsic thermal noise allows the ear to function as though close to 0K. Again, this suggests system properties inherent in the detection sequence. These "perfect" amplifiers could not be described by any chemical kinetic model nor by any quantum mechanical theory in which the random phase approximation is valid. The molecular dynamics of amplifiers in Bialek's models would require preservation of quantum mechanical coherence for times comparable to integration times of the detector. It is not known whether comparable mechanisms may determine electromagnetic sensitivities as a more general tissue property at cellular and subcellular levels.

Behavioral electrosensitivity in sharks and rays may be as low as 0.5 nV mm^{-1} for tissue components of electrical fields in the surrounding ocean (66). These marine vertebrates sense these fields through

specialized jelly-filled tubular receptors (ampullae of Lorenzini) up to 10 cm in length, located near the snout and opening on the skin surface through minute pores. Sensing nerve cells lie in the wall of this ampullary tube. In support of a cooperative model of organization of these neurons, behavioral electrosensitivity in sharks and rays is 100 times below measurable thresholds of individual electroreceptor neurons (67).

2. Domain Properties in System of Non-excitable Cells: Culture Dimensions and "Bystander" Effects

Jessup et al. (68) have pioneered studies on the role of gravitational fields in determining trends towards either apoptosis (programmed cell death) or towards cell proliferation. Concurrently, they tested the physical configuration of cell cultures in their influence on these same trends. Based on a colorectal cancer cell line, they compared cells cultured in adherent monolayers with three-dimensional (3-D) cultures.

Biochemical measures of apoptosis and cell proliferation were tested (1) in static cultures, (2) in cultures subjected to slow rotation, and (3) in cultures exposed to the microgravity of low-earth-orbital space flight. Over the course of 6 days on earth, static 3-D cultures displayed the highest rates of proliferation and lowest apoptosis. Rotation appeared to increase apoptosis and decrease proliferation, whereas static 3-D cultures in either unit gravity or microgravity had less apoptosis. Expression of the carcinoembryonic antigen (CEA) as a marker of cell differentiation was increased in microgravity.

For ionizing radiation, the U.S. National Council on Radiation Protection (NCRP) has recommended that estimates of cancer risk be extrapolated from higher doses by using a linear, no-threshold model. This recommendation is based on the dogma that the DNA of the nucleus is the main target of radiation-induced genotoxicity and, as fewer cells are directly damaged, the deleterious effects of ionizing radiation proportionally decline. Experimental evidence seriously challenges this concept (69). They used a precision microbeam of a particles to target an exact fraction (either 100% or ≤20%) of the cells in a confluent cell population and irradiated their nuclei with exactly one a particle each. The findings were consistent with non hit cells contributing significantly to the response, designated *the bystander effect*. Indeed, irradiation of 10% of a confluent mammalian cell population with a single a particle resulted in a mutant yield similar to that observed when all the cells in the population were irradiated. Importantly, this effect was eliminated in cells pretreated with 1 mM octanol, which inhibits intercellular communication mediated by gap-junction proteins. "The data imply that the relevant target for ionizing radiation mutagenesis is larger than an individual cell."

V. CONCLUSIONS

Epidemiological studies have evaluated ELF and radio-frequency fields as possible risk factors for human health, with historical evidence relating rising risks of such factors as progressive rural electrification and, more recently, methods of electric power distribution and utilization in commercial buildings. Appropriate models describing these bioeffects are based in nonequilibrium thermodynamics, with nonlinear electrodynamics as an integral feature. Heating models, based in equilibrium thermodynamics, fail to explain an impressive spectrum of observed electromagnetic bioeffects at nonthermal exposure levels. We face a new frontier of much greater significance.

In little more than a century, our biological vista has moved from organs to tissues, to cells, and most recently, to the molecules that form the exquisite fabric of living systems. We discern a biological organization based in physical processes at the atomic level, beyond the realm of chemical reactions between biomolecules. Much of this signaling within and between cells may be mediated by free radicals of the oxygen and nitrogen species. In their brief lifetimes, free radicals are sensitive to imposed magnetic fields, including microwave fields. Free radicals are involved in normal regulatory mechanisms in many tissues. Disordered free radical regulation is associated with oxidative stress diseases, including Parkinson's and Alzheimer's diseases, coronary heart disease, and cancer.

Although incompletely understood, tissue free radical interactions with magnetic fields may extend to zero field levels. Emergent concepts of tissue thresholds to imposed and intrinsic magnetic fields address ensemble or domain functions of populations of cells, cooperatively whispering together in intercellular communication and organized hierarchically at atomic and molecular levels.

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to low-energy emission therapy (LEET). Incident power density for MRI is highly dependent on frequency and pulse

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23 Electrical Stimulation of the Internal Globus Pallidus in Advanced Generalized Dystonia

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Figure 7 Cross-sectional view of female anatomy.

Figure 8 The NeoControl Pelvic Floor Therapy System.

Figure 9 Neotone device.

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Figure 5 Diskograms demonstrating the proximal and distal positions of the Arthrocare Wand as described in Fig. 4. (a)

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images showing the proximal and distal position of the Arthrocare Wand.

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A Boy and His Dog

(Heart Rhythms)

Figure 11 Heart rhythm patterns of a boy and his dog. These data were obtained using ambulatory ECG (Holter)

recorders fitted on both Josh, a boy, and Mabel, his pet dog. When Josh entered the room where Mabel was waiting and

consciously felt feelings of love and care towards his pet, his heart rhythms became more coherent, and this change

appears to have influenced Mabel heart rhythms, which then also became more coherent. When Josh left the room, Mabel’s

heart rhythms became much more chaotic and incoherent, suggesting separation anxiety!

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Figure 12 Seventy-two-year-old male with adenocarcinoma of the prostate and metastases to the ribs and pelvis

showing destruction of the pubis. (a) Treatment was started on July 7, 1997 with dramatic improvement in general well

being as well as osteolytic lesions in the pelvis after only 4 days. (b) On July 25 the reduction in metastases was even

more impressive. (c) The patient had to return to the United States where he intended to find a physician to continue the

treatment, but contact was lost because he was apparently unable to accomplish this. Reduction in metastases was even

more impressive.

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Figure 13 Seventy-five-year-old female seen on March 29, 1998 complaining of progressively severe abdominal pain,

weight loss, and fatigue for a month. Tomography revealed a malignancy of the body and head of the pancreas with

invasion of regional lymph nodes (a and b). She was started on diet, received polarizing solution twice weekly along

with daily application of 150 G to the affected area. She improved rapidly with respect to relief of pain, return of energy,

and weight gain, and her general condition was excellent 24 months later, (c) She continued to do well and tomograms

at 36 months showed no increase in the tumor size and necrotic areas could be seen (d and e). She was seen by an

oncologist who told her that the original diagnosis must have been an error since nobody with this type of pancreatic

cancer lives for 3 years, and she could eat as much salt as she wanted and discontinue the treatment. The patient was

pleased with this opinion and took his advice but died shortly thereafter.

Figure 14 (a) Before treatment, (b) after 2 months, (c) after 6 months, and (d) after 7 months.

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Figure 4 In large electric quantity group (100 C for 1.0 cm diameter), tumor cells were killed completely.

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Figure 5 Coagulatory necrosis around anode.

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Figure 6 Liquid necrosis around cathode area.

Figure 7 Experiment of ECHT on human lung cancer showed presence of tumor necrosis and much gas.

Figure 8 Experiment of ECHT on resected lung cancer to observe different biological effects of anode and cathode. It

showed that the killing effect of a cathode is stronger than an anode.

Figure 9 BK 2000 instrument of ECHT. Four outputs controlled by computer. AC 200-240 V, 50- 60 Hz, 150 W,

voltage: 0-25V+0.1V, electric current: 0-200mA+2mA, electric quantity: 0-9999 C. (The instrument is made by Prof.

Hongbin Pang.)

Figure 10 Electrodes made of platinum.

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