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Beneficial Effects of Electromagnetic Fields

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Abstract Selective control of cell function by applying specifically configured, weak, time-varying magnetic fields has added a new, exciting dimension to biology and medicine. Field parameters for therapeutic, pulsed electromagnetic field (PEMFs) were designed to induce voltages similar to those produced, normally, during dynamic mechanical deformation of connective tissues. As a result, a wide variety of challenging musculoskeletal disorders have been treated successfully over the past two decades. More than a quarter million patients with chronically ununited fractures have benefitted, worldwide, from this surgically non-invasive method, without risk, discomfort, or the high costs of operative repair. Many of the athermal bioresponses, at the cellular and subcellular levels, have been identified and found appropriate to correct or modify the pathologic processes for which PEMFs have been used. Not only is efficacy supported by these basic studies but by a number of double-blind trials. As understanding of mechanisms expands, specific requirements for field energetics are being defined and the range of treatable ills broadened. These include nerve regeneration, wound healing, graft behavior, diabetes, and myocardial and cerebral ischemia (heart attack and stroke), among other conditions. Preliminary data even suggest possible benefits in controlling malignancy.

Key words: cell function, magnetic fields, PEMF connective tissues, musculoskeletal disorders

A revolution is occurring in the ability to control specific aspects of cell function by precise physical means. This revolution goes far beyond the classically recognized mechanisms living systems have evolved to facilitate transduction of certain types of energy to functional responses, such as photochemical reactions (e.g., vision) and action potentials in nerve and muscle. During the past two decades, it has become increasingly clear that weak, non-ionizing electromagnetic fields exert a wide range of athermal effects when energetic patterns and "biotargets" are properly matched. As a result, a critical re-examination of weak field interactions with the charge and other physical characteristics of many biochemical species is in progress (e.g., ligand-receptors, phase transitions, and cooperativity, among others). Simultaneously, a new approach to medical therapeutics is emerging, one in which abnormal cell behavior is modified, beneficially, by inductive-coupling of selected, externally applied, extremely low frequency (ELF) magnetic fields.

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A major thrust for these developments derived from the clinical success of pulsed electromagnetic fields (PEMFs) in salvaging limbs scheduled for amputation, after repeated surgical failures to heal patients with chronically ununited, broken bones [Bassett, 1989; Bassett et al., 1974a]. Almost at the same time, certain types of time-varying magnetic fields were reported to affect calcium efflux and influx in brain tissue [Bawin and Adey, 1976]. Shortly, thereafter, epidemiological reports began to appear suggesting a link between cancer and 60 Hz power lines [Wertheimer and Leeper, 1979]. These three nearly concordant events stimulated scientific interest in the mechanisms of action responsible for these bioelectromagnetic effects.

Significant progress has been made in the past 15 years in defining many cellular and subcellular mechanisms of action when biosystems are exposed to a variety of ELF magnetic fields. More recently, effects at the level of the whole organism and the molecule have been reported [Blank and Soo, 1992; Reiter et al., 1992]. Not as much progress, however, has occurred in identifying the physical principles underlying athermal bioeffects. Although a number of physical mechanisms have been investigated, including

ion cyclotron resonance, parametric resonance, and, more recently, quantum effects on singlet-triplet states, bioelectromagnetics still lacks concrete explanations for weak ELF field effects. Until this issue is addressed successfully, some classical physicists will continue to claim that thermal noise overshadows any effect of a weak field. These individuals, currently, refer to repeatable bioresponses as "Pathological Science" and "the Emperor's Clothes." In the process, non-linear behavior, biomechanisms for increasing signal to noise (S/N) ratios (e.g., large, junctionally coupled cell arrays), and signal amplification through messenger responses at the cell membrane and its interior, among other factors, are ignored [Bassett, 1971, 1993; Pilla et al., 1992b].

It is not possible in this brief review of beneficial medical effects to cite the wide range of proven cellular and subcellular responses to different ELF magnetic fields. These have been reviewed elsewhere and, more recently, in the Proceedings of the 1st World Congress on the topic [Bassett, 1989; Blank, 1992]. Effects range from changes in cellular Ca^{++}, to modified receptor and messenger behavior, to increased synthesis and degradation. Highly specific alterations in transcription and translation have been reported, in which the energetic patterns of different fields (e.g., pulse shape and sequencing, frequency characteristics, amplitude, and spatial orientation, among other factors) produce functional "signatures" [Goodman and Henderson, 1991]. These and other data suggest strongly that there are "windows" and thresholds for bioeffects in which classic dose responses may not exist. Furthermore, data are emerging which indicate a direct interaction between the field and a gene without a cascade of biochemically mediated signalling (messenger) events being initiated at the plasma membrane or in the cytoplasm [Goodman et al., 1991]. In other words, isolated chromosomes, devoid of cell or nuclear envelopes, respond to field exposure. The mechanisms behind this behavior are moot but may involve resonance effects on ion counter charge at specific loci on the DNA molecule itself [Bassett, 1993; Hinsenkamp et al., 1978].

The pattern of bioresponse to field exposure depends not only on cell type, its state of function, and its tissue envelope but also on specific energetic characteristics of the magnetic field. Given this complex state of affairs, it is appropriate to address steps which led to specifications for the first therapeutic fields. These were derived from two decades of investigation focused on mechanisms to explain the exquisite sensitivity of bone cells to mechanical forces [Bassett and Becker, 1962; Bassett, 1971, 1989]. Bone mass and its spatial organization reflect load-bearing patterns with such precision that engineering principles can be applied to predict structure. Cellular action which selectively adds or removes bone in specific locations appears to be electrically mediated, through transduction. When bone and many other structural tissues are mechanically deformed, they become electrically charged as a result of piezoelectric, electret, and electrokinetic properties [Bassett, 1971, 1989]. The amplitude and frequency content of the resultant voltage waveforms reflect both the velocity and magnitude of the deflection. For physiologic loading, voltages between 10 μV and 1 mV/cm are produced with a frequency content predominantly in the range of <1 Hz to ≈ 100 Hz/or greater.

Electric field characteristics in these ranges have been shown to affect the function of bone (and other) cells, whether they arise endogenously from transduction or exogenously from inductively coupled, appropriately configured, time-varying magnetic fields [McLeod and Rubin, 1990]. The cell does not seem to make a distinction between the sources of the field, only its "informational" content. In fact, ELF magnetic fields can prevent the bone loss which normally occurs during immobilization, bed rest, or space flight (i.e., weightlessness) [Bassett et al., 1979]. These states diminish mechanical deformation, thereby reducing endogenous fields in the microenvironment of the cell.

Armed with the voltage patterns Nature appears to use to communicate instructions to bone, dynamic magnetic fields were designed to produce similar waveforms via inductive coupling. Specific details appear elsewhere [Bassett, 1989; Bassett et al., 1974b]. Suffice it to say, the term pulsed electromagnetic fields (PEMFs) was used to delineate these broad-band patterns within the larger electromagnetic spectrum. The fact that PEMFs proved to be a highly effective therapeutic agent for a range of musculoskeletal disorders may seem to be a striking example of the scientist's credo "it is better to be lucky than smart." For example, in the 20 years since the first clinical use of PEMFs, a variety of other field patterns have proven to be effective. On superficial examination, many of these have

widely disparate energy characteristics, although it appears that the induced electric field, rather than magnetic field component, exerts the main effect [Bassett, 1989, 1993; Pilla et al., 1992a]. When subjected to closer scrutiny (with methods such as Fast Fourier Transforms), however, there are many similarities or overlaps in frequency content and distribution [Bassett, 1989, 1993; Pilla, 1992; Stuchly, 1990].

The energetic principles for bioresponses being enunciated for therapeutic applications are beginning to spillover into the potential hazards of environmental fields. No longer is field intensity being viewed as the sine qua non for bioeffects; spectral analysis (e.g., frequency content) is now becoming a topic of focus and may well impinge on attempts to set health standards [Wilson et al., 1992]. Furthermore, it is increasingly clear that the passive electrical properties of different tissues may impose specific modifications in the characteristics of an induced voltage waveform. In other words, the frequency and amplitude patterns "seen" by a nerve or bone cell, residing in their respective tissues, can be quite different when exposed to identical PEMFs. "Signal processing" by a given tissue can alter frequency responses so that different "driving fields" appear as if they were electrically filtered [Bassett, 1989].

From a practical standpoint, therapeutic units, generally, consist of a portable, battery-powered pulse generator and a coil of wire which is placed, externally, over the site to be treated. Units are available only on a physician's prescription in the U.S.A. and have been approved for certain bony disorders by the F.D.A. since 1979. As current flows in the treatment coils, the resulting magnetic field penetrates the body (or cast or non-metallic brace), inducing a voltage and current in the exposed tissue. With present day clinical units, there is little or no evidence of a bioeffect in normal, resting tissues or cells within the field. Certain pathological processes, however, are modified, beneficially, if the PEMF "message" and exposure conditions are appropriate. Treatment times range from 20 minutes to 8–10 hours a day, depending on the nature of the abnormal process and applied field characteristics. Usually the equipment is fitted in the doctor's office and used at home. At least for PEMFs (i.e., induced voltage patterns similar to strain-generated waveforms), there is no discomfort or known risk. Compared with most alternative methods for treating bony disorders, the cost of medical care is significantly reduced because no hospital or surgical fees are involved.

In the two decades since PEMFs were first used for a patient with a chronically ununited fracture, more than 300,000 individuals, around the world, have been treated with the method. Domestically, clinical usage is restricted to those indications which are approved as safe and effective by the F.D.A. Nonunion, after fracture, failed joint fusions, and congenital pseudarthrosis (a highly recalcitrant, infantile nonunion, often associated with an inborn defect of nerves) fall into this category. Elsewhere, in the world, a number of other conditions, are being successfully treated with PEMFs, based largely on clinical findings in the U.S. but not yet approved by the F.D.A. Results in ununited fractures, in terms of success rates and treatment times, are essentially the same as those produced surgically [Gossling et al., 1992]. In some disorders, PEMFs are the only known method of successful treatment [Bassett, 1989, 1993].

Table I lists those medical problems in which PEMFs produce significant clinical benefits. All of these conditions currently encompass disorders of the musculoskeletal system or the integument. Clinical effectiveness, in each, has been proven by randomized, prospectively controlled studies and by double-blind trials. As can be seen in Table II, the mechanisms of PEMF action are appropriate to correct or modify the underlying pathological processes. Many of these mechanisms have been elucidated over the past 15 years, as the result of intensive tissue culture and animal studies. Despite the complexities of designing reproducible bioelectromagnetic experiments, more than a thousand reports of well-controlled studies underpin current understanding of cellular, subcellular, and biomolecular responses. In fact, as much or more is known about PEMF biomechanisms as is known about the action of aspirin.

Perhaps in no other arena of biomedical investigation are the requirements for precise interdisciplinary collaboration quite as rigorous as they are in bioelectromagnetics. Principles of physics, engineering, biology, biochemistry, physiology, genetics, and medicine all impinge on proper experimental design and interpretation. It is all too easy for biologists, unaware of the physical subtlities of field interactions with living systems, to fail in controlling or describing key elements of their exposure conditions. Conversely, it is all too easy for physicists and

TABLE I. Clinical Conditions Amenable to PEMF Treatment*

Condition	FDA approved	Controlled study	Treatment time	Success rate
Fracture nonunion	Yes	Prospective and double blind	3–6 mos	75–95%[a]
Failed joint fusions	Yes	Prospective	3–6 mos	85–90%[a]
Spine fusions	Yes	Prospective and double blind	3–6 mos	90–95%
Congenital pseuarthrosis	Yes	Prospective	6–12 mos	70–80%[b]
Osteonecrosis (Hip)	No	Prospective	6–12 mos	80–100%[b]
Osteochondritis dessicans	No	Prospective	3–9 mos	85–90%
Osteoporosis	No	Prospective	Life	85–90%
Osteogenesis imperfecta	No	Prospective	Life	—
Chronic tendinitis	No	Double blind	3–4 mos	85–90%
Chronic skin ulcers	No	Double blind	3 mos	85–90%

*Conditions currently unapproved by the FDA, in the United States, are being treated extensively elsewhere in the world with this technology. Results in osteogenesis imperfecta suggest a substantial reduction in fracture rate is possible in this rare pathological state and nonunions in these patients behave, during PEMF treatment, as they do in the general population.
[a]Rate dependent upon anatomical site and effectiveness of ancillary immobilization.
[b]Rate dependent upon severity classification.

TABLE II. PEMF Mechanisms of Action*

Condition	Pathology	PEMF cellular effects
Fracture nonunion	Soft tissues in gap, failure of calcification, bone formation and vascularization	↑ mineralization, ↑ angiogenesis ↑ collagen + GAG production, endochondral ossification
Failed joint fusion	As above	As above
Congenital pseudarthrosis	As above, plus ↑ osteoclasis	As above, plus ↓ osteoclasis
Spine fusion	Unincorporated bone grafts	↑ angiogenesis, ↑ osteoblastic activity
Osteonecrosis	Dead bone, rapid osteoclasis	↑ angiogenesis, ↓ osteoclasis, ↑ osteoblastic activity
Osteoporosis	↑ Bone removal ↓ Bone formation	↓ osteoclasis[a] ↑ osteoblastic activity
Osteogenesis imperfecta	Thin bones (osteopenia), Inborn error, collagen	↓ osteoclasis ↑ osteoblastic activity[b]
Chronic tendinitis	Avascular, hyalinized, fibrillated collagen	↑ Angiogenesis ↑ Collagen + GAG production
Chronic skin ulcers	Poor vascular supply and healing	↑ Angiogenesis ↑ Collagen + GAG production

*Many of these effects *may* derive from or are agumented by increased growth factors/mitogen production or "sensitivity."
[a]Reduced osteoclasis associated with reduction in collagenase activity and receptor responsiveness to parathyroid hormone.
[b]Metabolic error not corrected, but more bone means fewer fractures.

engineers to oversimplify exceedingly complex biosystems, so they can fit the standard equations of their disciplines. Table III lists some of the common confounders facing the physicist or biologist in designing bioelectromagnetic experiments. Those of us who study biosystems must develop a more universal recognition that all pervasive, weak, time-varying magnetic fields can affect their behavior, depending on energy characteristics and exposure conditions. Given this challenge, it is appropriate to ask whether most biological studies, since our Society became "electrified," have been conducted under truly controlled conditions. The few in which effective magnetic shielding (i.e., zero field conditions) has been used suggest strongly that some cellular functions are very different when they are isolated from ambient magnetic fields [Bassett, 1989; Dubrov, 1978].

At the present time, there are a number of important, rational, clinical extensions in the wings, waiting to be brought into the mainstream of medical therapeutics. Some of the more immediate breakthroughs are summa-

TABLE III. Interactive Factors Determining Bioelectromagnetic Responses

Physical	Biological
A. Primary ("driving") fields 1. Strength (Intensity) 2. Homogeneity (E vs. B) 3. Vectors (B_{ac} and B_{dc}) 4. Time-varying characteristics a. Rep rate and sequencing b. Pulse shape (symmetric or not) c. Rise and fall times d. Frequency content e. Switching transients B. Secondary (environmental) fields 1. Geomag. (static and time varying) 2. Switching transients (motors, etc.) 3. Electron microscopes, NMR, ESR 4. Powerlines 5. R.F. and microwave 6. Magnetic door catches 7. Electrostatic (fur, clothing) C. Endogenous electrogenic events 1. Fixed charge on moving membranes and organnelles 2. Action potentials 3. Transmembrane potentials 4. Injury potentials 5. Development potentials 6. Strain-generated potentials a. Piezoelectric b. Electrokinetic 7. Resultant biomagnetic fields D. Passive electrical properties 1. Solid state (rectification) 2. Ferroelectric ("memory") 3. Electrets 4. Capitance/impedence 5. Dielectric properties 6. Magnetite	A. Biofactors-cell 1. Size, shape 2. Density (confluent, non-confluent) 3. Junctions 4. State of function a. Dividing b. Resting c. Synthesizing d. Differentiated/specialized e. Embryonal/senescent f. Migrating 5. Exposure pattern a. Phasing in cell cycle b. Duration c. Continuous vs. interrupted d. Orientation in B and E fields B. Biofactors-tissue 1. Type 2. Microstructure (axes, planes) 3. Orientation in B and E fields 4. Hydration 5. Charged species 6. Mobility of charge carriers 7. Charge relaxation C. Biofactors-animal 1. Size (scaling) 2. Orientation in B and E fields a. Random b. Preferred c. Fixed 3. Local vs. systemic effects a. Melatonin b. Glucocorticoids 4. "Crosstalk" a. Shielding b. Distance 5. Stressors a. Vibration b. Electrostatic c. Restraint

rized in Table IV. Lest the reader be tempted to interpret this broad potential therapeutic spectrum as evidence that bioelectromagnetics is a panacea let it be said, there is no panacea. This discipline faces many challenges in determining the most propitious field characteristics for a given pathologic state. At the current state of the art, it is fortunate that the broad-band patterns chosen to open the therapeutic quest exhibit a capacity to produce a number of potentially beneficial bioresponses. As one examines known cellular mechanisms behind present day usage, many are similar and address some common abnormalities in each of the clinical settings. Furthermore, the role of the passive electrical properties of each tissue, interacting with the field to which it is exposed, impose certain highly specific changes in the energy characteristics an embedded cell will finally "see." These properties probably change as disease alters the structure and composition of the tissue.

Unfortunately, data supporting projections for clinical expansions are largely unknown outside bioelectromagnetic research. This situation can only be remedied by an educational outreach such as that epitomized by the Prospects series

TABLE IV. Experimental Data Supporting Some New Clinical Indications for PEMFs

Conditions	Supporting experimental data
1. Acute myocardial ischemia (heart attack)	Animal data showing decrease in infarct size, (acute effects on blood flow and angiogenesis, ? effect on superoxide dismutase, nitrous oxide)
2. Acute cerebral ischemia (stroke)	Same as above.
3. Cancer	Animal data demonstrate decreased growth and invasiveness of Meth A sarcoma in BalbC mice, encapsulation, cell and nuclear changes.
4. Dental (periodontal disease, edentulous jaw and extraction sockets)	Animal data show decrease in bone resorption in jaws, increased osteogenesis in tooth extraction sockets and an improved bacterial flora spectrum.
5. Diabetes (adult onset)	Clinical benefits on blood glucose reported, ? secondary to Ca^{++} effects on insulin secretion.
6. Diabetic and alcoholic neuropathy (insensate skin, ulcers, and charcot joints)	Effects on axoplasmic transport, neuronal protein synthesis, Ca^{++}/neurotransmitter effects at synapse, and angiogenesis.
7. Ligament/tendon healing	Animal data showing improved healing, increased collagen and GAG synthesis, increased angiogenesis.
8. Peripheral nerve transection and crush	Animal data showing increased protein synthesis, axon migration and function.
9. Spinal cord injury	No direct evidence but data bearing on neuropathy and nerve transection may prove beneficial, particularly in crush injuries when sensory and motor evoked potentials are still present.

in this journal. It is to be hoped through such endeavors the attention and involvement of those steeped in the more classic reaches of biology, biochemistry, biotechnology, and other similar disciplines can be convinced to add bioelectromagnetic principles to their experimental profiles. The ultimate payoff for physicians and their patients of such a development are potentially enormous. For example, preliminary findings suggest that bioelectromagnetics may hold a unique promise for modifying the malignant behavior of certain types of experimental cancer, athermally [Bassett, 1989].

Certainly, there seems to be little question that physical control of cell function is established as an embryonal facet of biology and medicine. Although many of the data supporting this view are born of direct interaction between certain field energetics and the cell, both synergistic and antagonistic modifications of drug, hormone, and growth factor-mediated effects are possible. In fact, the actions of Ca^{++} channel blockers, parathyroid hormone, and IGF-II, among others, already have been shown to be affected by weak time-varying magnetic and electric fields [Bassett, 1989, 1993].

This presentation has focused on athermal bioeffects of weak fields which have proven to be beneficial in medicine. Other important athermal effects, also, have been observed at higher field intensities. For example, with stronger intensities and appropriate time domain characteristics (e.g., dB/dt), it is possible to evoke action potentials in nerves and muscle, using external coils. This non-invasive technology has added a new dimension to medical therapeutic and diagnostic capabilities [Stuchly, 1990]. Electroporation, with high intensity, short duration electric fields, having secured a central role in biotechnology, is poised to aid in the introduction of pharmaceutical agents, transdermally, to produce high local concentrations [Weaver, 1992].

Unfortunately, in our pursuit of the biochemical secrets of the cell, its electrical dimensions frequently are destroyed or overlooked [DeLoof, 1986]. Until these dimensions are considered on a broader scale, many of the mysteries of living systems will remain hidden. As noted a century ago by the noted Belgian chemist, Ernest Solvay, "The phenomena of life can and should be explained by the action of only physical forces which govern the Universe, and that, among these forces, electricity plays a dominant role" [Solvay, 1894]. The surface of bioelectromagnetics has only been scratched, but beneath it there

appears to be considerable treasure to be discovered.

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