Low Energy Pulsing Electromagnetic Fields Modify Biomedical Processes

C. A. L. Bassett

Summary

Low-energy, pulsed electromagnetic fields (PEMFs) have reversed therapeutically resistant pathological processes in the musculo-skeletal system. Their development as a non-thermal therapeutic agent is based on 30 years of study of the electro-biological properties of connective tissues. Specific energy characteristics in applied PEMFs produce selected biological effects by modifying synthetic and other behavioral patterns of target cells; some mechanisms of action are defined. The technology appears safe and effective in clinical treatment of un-united fractures, avascular necrosis of bone, and chronic, refractory tendinitis. An expanding, rational use in biomedical science is predicted.

Introduction

Low-energy, pulsed electromagnetic fields (PEMFs) were first applied therapeutically 13 years ago at Columbia. A child with a fractured tibia, un-united after 12 operations over a 10-year interval, was facing amputation. The underlying problem, congenital pseudarthrosis (a "false joint") of the tibia, typically is resistant to surgical and non-surgical intervention. For the six months prior to starting PEMFs she was in a cast, on crutches, without X-ray evidence of healing. The only modification of management was to add a pair of energized wire coils opposite the break. Within 4 months healing occurred, and since then her united tibia has allowed participation in young adult activities.

In the intervening 13 years, this surgically non-invasive approach has proven riskless in more than 100 children with this rare condition. Dr Clinton Compere, in an editorial entitled Electromagnetic Fields and Bones, wrote: "...from my own observations one of the most dramatic effects of these [i.e. electrical] procedures has been on congenital pseudarthrosis." Dr Harold Boyd stated: "One would not applaud a 40% failure rate; however, this is superior to the results which follow the first operation - and may surpass the results of repeated operations. These views are shared by others, all of whom have cited the biological effectiveness of PEMFs in producing bony union in congenital pseudarthrosis.

Chronically un-united fractures in adults, also, are therapeutic challenges, albeit less than congenital lesions. More than 60,000 have been treated safely, as outpatients, with an overall success rate of 80% or more and with a significant economic advantage over surgical approaches. Many unhealed patients were > 2 years after injury actively infected and had had > 3 unsuccessful surgical repairs. Amputation had been recommended frequently for these patients, in whom spontaneous healing is exceedingly rare. As a control for this remote possibility, casts were applied to long-standing non-unions of the tibia, the patient placed on crutches, and serial X-rays taken for 3-4 months. No evidence of healing began until 1 to 2 months after PEMFs were started as the sole change in management. Similar findings recently were reported in a series of 147 patients who had failed to heal with external skeletal fixation.

Concomitant with extensive clinical use of PEMFs, in which more than 10,000 American orthopaedic surgeons have participated, a number of laboratories studied biological effects in animal and culture models. These confirmed that PEMFs affected cellular processes pertinent to bone repair. Before considering these results, it is appropriate to review well-established features of fracture healing.

Cell Responses to Fracture

Initially, an 'explosion' of DNA synthesis and cell proliferation occurs between the dense bony cortex, flanking the break, and the ensheathing periostium. Sleeves of new bone, the anchoring callus, are deposited proximally and distally. Opposite the break, an influx of young connective tissue cells form fibrocartilage, linking the sleeves of newly formed bone with a rubbery bridging callus. Progressive calcification of the bridge permits penetration of new vessels, removal of calcified fibrocartilage and its centripetal replacement by young fiber bone. This sequence, endochondral ossification, is closely akin to events occurring in growth centers. After the bone ends are mechanically joined by hard tissue, 'stress-working' (remodelling and maturation) proceeds in 95% of fractures. Early phases of repair occur in the presence of electrical currents of injury which have been postulated to trigger healing.

In chronically un-united fractures (non-unions), injury currents have subsided, unless re-injury occurs. The provisional bridge of soft tissue, opposite the fracture, is not calcified. Failure to complete this critically important step blocks later stages of repair, since vascular penetration of uncalcified fibrocartilage does not occur.

Mechanism of Action; PEMF Effects on Calcium

The pathologic features of non-union suggest that initiation of calcification will 'restart' the stalled, final phases of fracture repair. In fact, surgical methods to treat non-unions by plates or with bridging bone grafts achieve this end. PEMFs produce similar effects. Changes in cellular calcium content and calcification have been confirmed in a number of experimental systems and in patients. These responses appear in canine models of non-unions and in chick chondrocytes in tissue culture. Effects on calcification were confirmed in the U.K. by Fitton Jackson, at the Strangeways Research Laboratory in Cambridge. Several other reports indicate that PEMFs affect local mineralization processes but not total body calcium metabolism. Modifications in cellular calcium, also, have been implicated in several biological effects of PEMFs. These include rapid alterations in adenylcyclase and phosphodiesterase, depression of DNA synthesis in phytohemagglutinin-stimulated lymphocytes, altered division rates in Paramecium, increased collagen production and reduced lactate in fibroblasts, modified proteoglycan synthesis.
and decreased insulin secretion by pancreatic cells, among others. Investigators have noted similarities in PEMF effects and the calcium-blocker action of Verapamil. Later, endochondral ossification and bony bridging are confirmed, both radiographically and microscopically (Fig. 1). These clinical data are entirely consistent with experimental results. The mechanism of action is unknown, so all results are suspect. (2) Several different types of pulses have been reported to be effective: claims for specific action, therefore, are open to question. (3) Negative bone-healing experiments with PEMFs contradict both positive *in vitro*/*in vivo* experiments and clinical results. (4) A 'double blind' study of patients with non-unions has concluded that immobilization, alone, produced effects equal to PEMFs.

The first of these arguments has been answered already, in the preceding section, and the remaining three will be rebutted in order. First, certain physical and biological details, central to the debate, should be considered since many biologists and physicians are more familiar with biochemical than with bioelectrical phenomena. Even in physics and electrical engineering, specialists deal with specific field characteristics and design. Few of these experts have a working knowledge of biology or medicine. In an interdisciplinary vacuum, it is possible to think the world flat!

**PEMF Characteristics**

The acronym, PEMFs, is not meant to be generic for all electromagnetic fields. It is restricted to pulse types in common clinical usage to treat unhealed fractures and other pathologic processes. Each of these pulses simulates the shape and amplitude of asymmetric electrical waveforms detected when bone is dynamically deformed (Fig. 2). These electromagnetic phenomena in bone have been well characterized in the past 25 years, and electrical responses to mechanical deformation appear to result from piezoelectric and electokinetic (streaming potentials) behavior and are postulated to provide feedback control of cell behavior during stress-related remodelling (Fig. 3). The pulses used in PEMFs are quasi-rectangular or quasi-triangular when the voltage waveforms are recorded by a standardized coil-probe dosimeter (Fig. 4). Their repetition rates lie in the extremely low-frequency (ELF) range. When analysed by discrete Fourier transforms, these several waveforms share some frequency-content characteristics and
CHALLENGES

all can be categorized as ‘broad-band’. Depending upon the rise and fall times, the specific shape, the amplitude and the rate of repetition, single pulses or pulse burst quasi-rectangular waveforms contain frequencies ranging from ≈ D.C. to ≈ 10 MHz (Fig. 5).

Although each of the two quasi-rectangular pulse patterns has its own individual frequency-content profile, there are common ranges in both. Other PEMFs, characterized by quasi-triangular waveforms, also contain frequencies which overlap. Gaussian white noise, centered on the frequency range found in quasi-rectangular and quasi-triangular pulses, applied to patients with fresh fractures, increases technetium polyphosphate incorporation significantly.

Whilst effectiveness of different waveforms may derive from common physical features, rigorous assessment of relative efficacy has yet to be made in a non-union model. None the less, alterations in pulse specifications can selectively modify calcification during repair. It is conceivable that the situation, ultimately, may prove analogous to the relationship between penicillin G and ampicillin. Both pathways do not, necessarily, involve feedback. The left-hand vertical and the central pathways concern mainly ultra- and extremely low-frequency events and the right-hand pathways represent higher frequency events. The left-hand low-frequency pathways may be permissive for action of higher frequency content, through electrical biasing.

pulses trigger an 11-fold increase in mRNA within 15 minutes, but bursts produce control values. Selected pulse modifications appear to activate gene-specific transcription and translation. Embryonic development (e.g. DNA and dry weight of bones) of the chick is influenced in different ways by different pulse patterns. Single pulses and bursts affect collagen and proteoglycan synthesis, selectively, depending on whether the target tissue is bone or cartilage.

Dominant sine wave frequencies have been identified in Fourier-transformed broad-band pulses. By substituting one or more of these sine patterns for a PEMF, contributions of certain individual frequencies have been identified. They are postulated to operate within normal control systems and may involve balances between synthesis and degradation. Within a broad-band pulse, selected frequencies could affect both activities, depending upon the functional state of cells during PEMF exposure. For example, cultures in growth and confluent phases respond differently. Length of exposure to PEMFs, also, appears to be important in certain systems. PEMF-triggered transcription is significantly less after 45 minutes than after 15 minutes.

Windows or thresholds for different biological effects of time-varying fields were suspected to exist over a decade ago. PEMF windows appear to encompass more factors than dose response alone. Frequency, amplitude and timing, singly or in combination, appear to be involved in many of the experimental studies cited above. Windows appear, also, to determine calcium release by brain and other in ELF, sine-modulated 50 and 450 MHz carrier-wave fields.

Unfortunately, few publications contain sufficient details to permit window duplication in non-sinusoidal field experiments. Unless standardized PEMF equipment is used, pulse shapes should be specified in air or in target tissues, using a universally acceptable dosimetric technique. Dosimeters should have a good frequency response from D.C. to at least 10 MHz. Even detailed descriptions of circuits are insufficient; significant variations in fields can arise from different coil designs and circuit components (e.g. capacitors, resistors, solid-state devices). Current delivered to the coil(s) by different units constructed from the same circuit diagram can vary in subtle details of frequency content unless constructed with rigorous control and ‘tuned’ to desired

---

Fig. 3. Diagram of hypothesized, unified pathways relating various electrical, magnetic and mechanical influences on cell function. Cycle A represents a feedback pathway for Wolff’s law, which links bone form and function. This cycle may also apply to other tissues, such as connective tissues and plants for action of higher frequency content, through electrical biasing.

---

Characters in pulsations may derive from common physical features, rigorous assessment of relative efficacy has yet to be made in a non-union model. None the less, alterations in pulse specifications can selectively modify calcification during repair. It is conceivable that the situation, ultimately, may prove analogous to the relationship between penicillin G and ampicillin. Both pathways do not, necessarily, involve feedback. The left-hand vertical and the central pathways concern mainly ultra- and extremely low-frequency events and the right-hand pathways represent higher frequency events. The left-hand low-frequency pathways may be permissive for action of higher frequency content, through electrical biasing.
tolerances. Once in use, monitoring of signals is necessary because circuit components 'age' with use.

Athermal Nature of PEMF Action

Before pertinent physical principles are discussed, the issue of heating should be considered. The total energy input from PEMFs, with burst-type quasi-rectangular shapes, is $10^{-9}$ W/mm$^3$ of tissue. At nominal impedances, the temperature change is $< 0.001$ °C. Indeed, tissue culture experiments, with temperature carefully monitored, detect negligible thermal changes from PEMF exposure. If heating occurs, depending on pulse characteristics, it derives from easily measured and controlled ambient changes caused by coils, not from energy dissipation in cells or tissues. Additional evidence of athermal action stems from recent studies with Scalpia coprophila chromosomes, in which heat-shock responses are well characterized. PEMFs produce quite different patterns of transcription of mRNA and of translation. If fields, other than PEMFs, are sufficiently high in frequency and amplitude, thermal effects can occur. When they do, it is difficult to separate electrical and thermal contributions to results. For example, brief application of pulsed 27.8 MHz fields elevates body temperature by $2^\circ$C during neural regeneration experiments.

Characteristics of Inductively Coupled Fields

Physical parameters of a PEMF investigation must be controlled and matched to an appropriate biological model. Lack of reproducibility from study to study and laboratory to laboratory can be attributed, in the main, to lack of familiarity with critically important field characteristics. In any PEMF, both magnetic ($B$) and electric ($E$) field components exist. Inductive coupling of a time-varying $B$ field with electrically conductive elements in biological systems (mainly ionic) results in $E$-driven pulsed currents within the organism. Although the $B$ component may prove to affect certain cell functions, the $E$ component appears to be a major factor in PEMF results, to date. In accord with Maxwell's equations $\nabla \times E = -\frac{dB}{dt}$, both $B$ magnitude and its rate of change (i.e. rise and fall times) determine the $E$ value. This value, also, reflects position in the $B$ field, being zero in the center axis of a Helmholtz field and increasing by $1/2r$, peripherally. Furthermore, $E$ has a vectorial quality which imposes constraints on position and orientation of the target if reproducibility is to be achieved. Thus, when a biological system is exposed to a given pulse it may respond in one manner if parallel to $B$, another at right angles to $B$, another in the central axis of $B$ and yet another if peripherally located. When non-uniform fields are employed, complexity is increased.

Any experiment designed to test a given PEMF, also, may be influenced by extraneous weak time-varying geomagnetic and man-made fields. Dubrov called attention to work demonstrating that organisms in magnetically shielded environments display altered metabolic patterns. More recently, one rate of Ca$^{2+}$ efflux from brain tissue occurred when the Earth's time-varying magnetic field (measured in gammas, i.e. $10^{-6}$ Teslas) was nulled and another when it was not. Similarly, RNA synthesis...
CHALLENGES

was affected by PEMFs emanating from equipment several meters distant to an unshielded incubator in which 'control' studies were being conducted. In vitro studies in which control dishes and active coils are in the same incubator should be carefully scrutinized. This is particularly true if controls are placed in inactive coils which function as an antenna.

Furthermore, when unshielded incubators house control cultures, stray fields should be monitored. A recent study of weak sinusoidal field effects on DNA synthesis (as judged by [3H]thymidine incorporation) contained no detail on this point, nor on the cell counts which were necessary to judge the origin of the increased isotope uptake (e.g. nuclear or mitochondrial).

Stray fields, active coils. Stray fields, lateral anatomic sites serve as controls for regions being treated with active coils.

PEMFs – Pro or Con? II

During this presentation, two of the four arguments advanced by PEMF antagonists were considered. First, at least one pertinent mechanism of action for non-unions is defined. Second, PEMF waveforms used for non-unions are broad-band and are members of a putative dummy machines. Placebos should not contain a small amount of the active factor! Hopefully, broader interdisciplinary grasp of physical and biological variables will foster greater care in design and interpretation of future experiments. Failure to increase precision will only retard progress of this new therapeutic tool, which has a broad potential to improve patient care in many, if not all, medical specialties.

Expanding Clinical Indications for PEMFs

Progress has been made already in expanding the use of PEMFs outside the non-union arena, using pertinent biologic responses to selected PEMFs, as demonstrated in the laboratory or clinic. Avascular necrosis (osteonecrosis) of the adult hip and Legg–Perthes disease in children have been treated successfully. The biological activity of PEMFs and their clinical usefulness in therapeutically reacclimatizing tendinitis of the shoulder have been proven in a double-blind study with P < 0.005.

A pilot study of patients with postmenopausal and senile osteoporosis and laboratory observations appear to justify double-blind studies of PEMFs' ability to restore bone mass. Selected PEMFs improve the rate of peripheral nerve regeneration and function. Promote growth of new small blood vessels (angiogenesis) and modify the local action of certain hormones. These laboratory observations await clinical evaluation in patients with severe nerves and neuropathies, and with marginal circulation in skin grafts and the myocardium.

Unlike investigations with new drugs, these clinical endeavors will not impose known risks. PEMFs have proven to be remarkably safe in broad human application over the past 10 years. No toxicologic or teratologic effects have been demonstrated in extensive in vitro and in vivo safety testing. This is not to say that all time-varying magnetic fields share the same record of safety. The energetics of other parts of the electromagnetic spectrum, for example radio frequency (R.F.), microwave and X-ray, can be harmful. Even at the lower end of this spectrum, certain frequency combinations may produce deleterious effects in some biological systems. Recent observations of possible human teratologic action of electric blankets and the impact of other types of time-varying fields on chick embryo development dictate the need for due diligence. Certainly, a clearer definition of field parameters by all concerned will help dispel some of the 'hysteria' now developing in a near vacuum of precise knowledge. With care and a bit of luck, the next decades can witness an era of electrobiological achievement which may rival that of molecular biology.

REFERENCES

The standard editorial policy of BioEssays is to limit the number of literature citations to 30. However, exceptions are occasionally made for articles that deal with controversial issues. The subject covered by Dr Bassett is in this category. For this reason, a significantly longer than usual list of references has been assembled, to permit readers to refer to the original publications rather than reviews, the better to form their own opinions about the state of the work.

5. Sutcliffe, M. L. & Goldberg, A. A. J. (1982). The treatment of congenital pseudarthrosis of the tibia with pulsing electro-
united tibial diaphyseal fractures with pulsing electromagnetic fields. J. Bone Jt. 
netic field treatment in ununited fractures and failed arthrodeses. JAMA 247, 
623–628.
8 MARCER, M., MUSATTI, G. & BASSETT, C. A. L. (1984). Results of pulsed electro-
magnetic fields (PEMFs) in ununited frac-
9 SIMMONS, D. J. (1980). Fracture healing. In Fundamental and Clinical Bone Physi-
rents traverse intact and damaged bone. Science 225, 478–482.
13 BRIGHTON, C. T. & HUNT, R. M. (1986). Ultrastructure of electrically induced osteo-
14 MULLER, J., SCHENK, R. & WILLENEG-
GER, H. (1968). Experimentelle unter-
suchungen über die einstellung reaktiver 
pseudoarthrosen am Hunderadius. Helv. 
15 BASSETT, C. A. L., CHOKSHI, H. R., 
HERNANDEZ, E., PAWLUK, R. J. & STROP, 
M. (1979). The effect of pulsing electro-
magnetic fields on cellular calcium and calci-
fication of non-unions. In Experimental 
Magnetic Field Effects on Cellular Calcium and Calcium 
Metabolism and Calvaria Resorption 
(eds. D. W. Adey, M. A. Well-Chater, C. 
& PERRIN, S. M. (1980). Prophylaxe des pseud-
arthrosen durch magnetische stimulation? Unfall-
hilfenkunde 83, 189–194.
17 COCHRAN, G. V. B., PAWLUK, R. J. & 
19 MARSLAND, T. P. (1985). Biophysical studies of pulsed magnetic field interaction 
with biological systems: part II, physical effects. NATO ASI Series 97, pp. 547–555. 
21 BASSETT, C. A. L., VALDES, M. G., 
HERNANDEZ, E. (1982). Modification of 
fracture repair with selected pulsing electro-
magnetic fields. J. Bone Jt. Surg. 64-A, 
888–895.
22 GOODMAN, R., BASSETT, C. A. L. & 
HENDERSON, A. S. (1983). Pulsing electro-
magnetic fields induce cellular transcrip-
23 GOODMAN, R. & HENDERSON, A. S. 
(1986). Some biological effects of electro-
magnetic fields. Bioelectrochem. Bio-
eng. 14, 83–91.
24 FARNDALE, R. W. & MURRAY, J. C. 
(1985). Pulsed electromagnetic fields pro-
mote collagen production in bone marrow 
ﬁbroblasts via athermal mechanisms. Calcif. 
Tissue Int. 37, 178–182.
25 MURRAY, J. C., CHOKSHI, H. R., 
Modification of collagen production in 
cultured ﬁbroblasts by a low-frequency, 
pulsed magnetic ﬁeld. Biochim. Biophys. 
pulsed electromagnetic field on a mixed 
167, 280–290.
 tromagnetic ﬁeld effects on chondroblasts 
28 ROOZE, M. A. & HIIJSENPAM, M. G. 
(1982). Histochemical modiﬁcations in-
duced in vitro by electromagnetic stimu-
lization of growing bone tissues. Acta 
Orthop. 181, 278–282.
30 JOLLEY, W. B., HINSHAW, D. B., 
PHILANDER, S. M. (1980). Results of 
pulsed electromagnetic ﬁelds used in the stimulation of bone fracture 
31 RINSEY, L. A., HALPERN, A., SCHU-
Biophysical principles affecting bone structure. In Bio-
32 BASSETT, C. A. L. (1978). Pulsing electromag-
netic fields: a new approach to surgical 
problems. In Metabolie Surgery (ed. Henry 
33 MURRAY, J. C. (1982). Pulsed electro-
172, 287–292.
34 ADEY, W. R. (1977). Models of mem-
branes of cerebral cells as substrates for 
information storage. Biosystems 8, 163–178.
and Bone. Lancer i, 815.
The effects of pulsed magnetic fields of the 
type used in the stimulation of bone fracture 
37 ENZLER, M. A., WEALECHI-SUTER, C. 
& PERREN, S. M. (1980). Prophylaxe des pseud-
arthrose durch magnetische stimulation? Experimentelle überprüfung der methode 
nach Bassett an Beagle-Hunden. Unfall-
hilfenkunde 83, 189–194.
38 BASSETT, C. A. L. & BECKER, R. O. 
(1962). Generation of electric potentials in 
39 COCHRAN, G. V. B., PAWLUK, R. J. & 
moisture conditions. Clin. Orthop. 58, 
249–270.
tials in fluid-saturated bone. J. Orthop.
Res. 1, 30–41.
41 MARSLAND, T. P. (1985). Biophysical 


C. A. L. BASSETT is at the Department of Orthopaedic Surgery, Columbia Presbyterian Medical Center, 2600 Netherland Ave, Riverdale, New York 10463, USA.

\section*{PLACES}

\section*{Instituto de Investigaciones Bioquimicas ‘Fundación Campomar’: The new laboratories of Luis F. Leloir}

Clara R. Krisman-Fischman and W. J. Whelan

Luis Federico Leloir, the 1970 Nobel Laureate in Chemistry, distinguished for his researches in carbohydrate metabolism, notably for the discovery of the nucleoside diphosphate sugars, celebrated his 80th birthday on 6 September 1986. Typical of his shyness and his wish to avoid the public eye, he was nowhere to be found when the day came. His career, its fortunes and vicissitudes, epitomizes the struggle of basic biological scientists to gain a secure footing in his native Argentina and demonstrates how a wealth of talent can emerge under the patronage of exemplary, steadfast, caring and unselfish leadership.

A pupil of Bernardo Houssay, himself a Nobel Laureate in Physiology or Medicine, sharing the Prize in 1947 with Carl and Gerty Cori, Leloir, working under conditions that would have dismayed and discouraged most others, has been the inspiration and beneficent ‘Dire’ to generations of Argentinian biochemists and the lifeline without which many careers would have founded. His scientific achievements have been documented in numerous places, sometimes by himself, in his self-effacing way, when his shyness and humility come through. This account, in our ‘Places’ series, uses the occasion of his milestone birthday to describe the new laboratories where he is the President of the administrative Council.

Returning from sojourns in the laboratories of Frederick Gowland Hopkins in Cambridge and Carl Cori in St Louis, to an Argentina that in 1943 had experienced a revolution and in 1946 was to be ruled by General Peron, Leloir was confronted by a situation in which university professors were forced to resign and go into exile. Others, like Houssay and Leloir, decided, with help from the private sector, to remain, and in doing so created first-rate institutes which gained international renown.

Then in 1947, Don Jaime Campomar, a prominent textile manufacturer, provided funds for the creation of the Instituto de Investigaciones Bioquimicas which, in memory of his parents, Juan and Maria Scasso de Campomar, was named the ‘Fundación Campomar’. Its statutes define the