ACCELERATION OF FRACTURE REPAIR BY ELECTROMAGNETIC FIELDS. A SURGICALLY NONINVASIVE METHOD

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INTRODUCTION

During the past 15 years, a variety of biological systems have been found capable of transducing mechanical to electrical energy.[1-3] This behavior, generally, has been ascribed to piezoelectric-like properties of long-chain biopolymers. These include collagen, cellulose, keratin, protein polysaccharides, and nucleic acids, among others. Although the generic term "piezoelectric" has been used to describe the behavior of such biopolymers when they are mechanically deformed, it is evident that charge separation in these compounds may occur on the basis of other biophysical properties.[1,4,5] For example, pyroelectric, ferroelectric, solid-state, and electret properties have been found to exist in polymeric constituents of cells and extracellular matrix.

Because mechanically induced charge separation is a fundamental phenomenon in most or all biological systems, it is pertinent to determine whether electrical activity of this type has functional significance. Although there is a paucity of "hard" data, there are many physiologic processes that, hypothetically, can be affected. A partial list of some of the more important cell functions and properties is as follows:[1] replication of DNA and protein synthesis; the availability of unbound cations and anions; membrane permeability, adhesiveness, and mobility; enzyme and hormone function; the function of contractile proteins (including microtubules and similar structures); cell-to-cell communications; the state of structured biowater; and mitrochondrial function and redox systems. At the extracellular level, mechanically induced charge separation, conceivably, may affect the alignment and "reactivity" of charged biopolymers, the physical properties of tissues, and the regulation of cell nutrition.[1,6,7] Speculation of this nature is justified if it serves to focus the attention of investigators, within and without biology, on the need to devise critical experiments to provide "hard" data. It is the purpose of this article to give examples of potential benefits to be derived from hypotheses of this type and to document how they stimulated a search for a practical method to accelerate the process of fracture repair.

In 1962, mechanically induced charge separation was hypothesized to control the activity of osseous cells and their biopolymeric byproducts.[8] Subsequent to 1964,[1,6,7,9] this concept was expanded to encompass a cybernetically based, negative feedback control system that operates as the basis for Wolff's law. To place the original proposals on firmer ground, experiments were devised to document that "weak" electrical events, of a magnitude observed in deformed bone, could affect the behavior of bone cells. This attempt was made with knowledge that Japanese investigators had reported in the 1950s that bone formation could be stimulated electrically.[10–12] Details of those investigations, however, were incomplete, and serious questions with respect to controls and electrode effects were left unanswered. The new series of studies, undertaken in 1963–4,[13] utilized miniaturized, implantable battery "packs" with platinum-iridium electrodes. When implanted in the medullary canal of dogs, increased osteogenesis was observed around the cathode when a current of 3–4 μA was established for 21 days. Observations and techniques established during those experiments have served as a model for many similar investigations in the past 9 years. These included a study, in these laboratories, of constant current, pulsed current with both symmetric and asymmetric duty cycles, and polarities,[14] repetition of the original dc currents,[15–17] a thorough study of constant currents,[18] and studies of the effects of constant-current pulses[19,20] and of ac signals.[21] From these several sources, the following observations seem to be established. First, osteoblastic activity characteristically is observed near the electrode that is held cathodic under dc conditions, while osteoclastic activity may be present under mild anodic conditions. Second, there is a "threshold" current of 3–5 μA necessary to stimulate osteogenesis in these systems. An "optimal" stimulus exists in the range of 10–25 μA. Third, deleterious effects appear when currents larger than 50 μA are employed. Fourth, in most cases, under pulsed or ac conditions, a polarity-dependent cellular response (osteoblastic vs osteoclastic) is not observed.

It is clear that, since electrode materials ranging from platinum-iridium to stainless steel are in intimate contact with cells, extracellular matrices, and fluids, various electrolysis effects, probably, are always present.[22] For example, when a stainless steel electrode is under sufficiently anodic conditions, a significant concentration of foreign (and usually toxic) ions will build up in the extracellular environment. Even platinum ions will appear in solution under these conditions. At sufficiently high dc currents, both anodic *and* cathodic electrolysis products can be deleterious. Under pulsating and ac conditions, it becomes easier to avoid net electrolysis by a careful choice of duty cycles and potential control.[22,23] The result of the electrolysis effect is that it becomes increasingly difficult to dissociate secondary electrochemical phenomena that occur at the implanted electrodes from those that may appear as a direct result of electrical stimulation. *In vitro* studies of electrochemically mediated morphological and functional changes in the amphibian erythrocyte were based on the studies of Becker and Murray[34] and were specifically aimed at the above problem. These results, which focus on a dynamic approach to *in vivo* interfacial electrochemical phenomena that occur between a cell and its environment, demonstrate that the effects are indeed caused by a change in the electric environment. Potentiostatically controlled, pulsing conditions, with a variety of electrode materials, were used in these studies. By comparison with dc stimulation of erythrocytes, it has been possible to implicate specific specific inorganic cations that may be involved in binding (specific absorption) at certain cytoplasmic and membrane sites.

The observation that electrically negative regions are associated with bone

formation and positive (or, possibly, electrically neutral) regions with bone resorption appears to correlate with other laboratory and clinical findings. For example, it is known that osteoblastic activity occurs on the concave surface of a bone, the surface which becomes electronegative on bending.[8,24–27] Conversely, osteoclastic activity appears on the electropositive or convex surface. Similarly, when teeth are subjected to orthodontic forces, formation is present in regions of negativity, at the "trailing" edge of the tooth, and resorption in positive regions (at the "leading" edge).[28] When these data are coupled, however, with the observation that little or no cellular "polarity" has been found in the presence of constant current pulses[19,20] or induced ac signals in fracture healing,[21] the significance of electrical "sign" must be reexamined.

Cellular responses in bone remodeling have been dissociated, in these laboratories, from those in bone repair to fashion a "working hypothesis." In this hypothesis, remodeling is viewed as being spatially oriented and accomplished by discrete cellular responses (osteoblastic and osteoclastic) over relatively long periods of time. In such a system, a series of electrical signals with a net negativity may well be required to direct formative processes, whereas signals with a net positivity direct destructive processes. The early phases of fracture repair, on the other hand, are rapid and result in deposition of callus in which the structural elements are poorly oriented to meet the mechanical demands of the whole bone. Such a repair process may require only a trigger signal, with little or no "directionality" (polarity) to initiate cell activity. With advancing maturity, however, the callus is subjected to deformation, and, as mineralization increases, internal stresses will result in electrical signals with polarity. These, in turn, conceivably can direct the remodeling that is known to occur. This hypothesis, clearly, requires buttressing with substantially more data than currently are available before it can be accepted.

Until 1964, it seemed possible to retard osseous repair processes but not to accelerate them. The demonstration of increased osteogenesis by dc stimulation, however, suggested that it might now be possible to speed up fracture healing by electrical stimulation. Conversely, this clinically attractive idea was modified by two major problems. First, bone formation, electrically induced by direct currents, was limited to discrete regions around the cathode, a region in which possible deleterious electrolysis effects might exist. Early attempts to expand significantly the magnitude of this response were unsuccessful. It, therefore, was postulated that if the method were applied to the larger bones of man, multiple electrodes would be required to produce a clinically significant bulk of callus in a brief time. Second, and more important, the method was surgically invasive. It either would require implantation of electrodes and circuits at one operation and their retrieval at another or the use of transcutaneous electrodes. The latter could well be associated with an increased incidence of bone infection.

The vast majority of fractures in this country can be treated successfully by closed reduction and plaster fixation. It seemed advisable, therefore, if electrical stimulation were to be used to accelerate fracture healing, that a surgically noninvasive method be developed. If a practical approach of this type could result in a 40–50% reduction in disability time without undue hazard to the patient, a considerable drain on the nation's resources might be alleviated. Fractures and other musculoskeletal injuries constitute the third largest group of disabilities that require hospitalization in this country. Furthermore, the cost of medical bills, third-party carrier involvement, compensation, liability, and loss of productivity is counted in the billions of dollars each year.

Accordingly, a search was begun in 1967 for a practical, safe, and efficacious

method to change the electrical environment of a fracture, without surgical intervention. The first approach was made in tissue culture studies. Electrostatic (constant) and electrodynamic (pulsing electrostatic) fields were assayed for their effects on the functional behavior of connective tissue cells *in vitro*. As a result, it was reported in 1968[29] and subsequently[1] that 3-T-6 fibroblasts, grown in Falcon petri dishes, responded to these capacitatively coupled fields with increased DNA and collagen synthesis. Electrostatic fields of 1000 V/cm were capable of increasing DNA synthesis by 15–20% and collagen production (as measured by [^{14}C]- and [^{3}H]proline conversion to hydroxyproline) by 50%. When exposed to 1 Hz electrodynamic fields at 1000 V/cm, DNA increased 20% above control values and collagen by as much as 300%. Concomitantly, a variety of ultrastructural changes, associated with increased synthesis, were documented in the experimental cells by means of electron microscopy.[1] Stimulatory effects were found in this system for field values as low as 100 V/cm, although at lower field strengths the effects were considerably diminished. Somewhat similar results recently have been reported by Norton and Moore.[30]

On the basis of these experiments, we elected to apply the system to fracture repair.[32] The model chosen for the investigation was a midfibular osteotomy in the rabbit. Because we decided to permit the animals free range, without tethering, equipment size and weight restrictions precluded use of the most effective field, namely, the 1000 V/cm 1-Hz electrodynamic stimulation. A 100 V/cm electrostatic field, therefore, was chosen for these initial studies. It was developed across the hind limb by means of two Mylar®-insulated brass plates, which were attached to Lucite® carriers and mounted with a 0.5-cm air gap between the plates and skin, medially and laterally. On the active legs, plates were attached to a 100-V battery source, and on the contralateral control legs, no electromotive force was provided. Animals were sacrificed after 21 days. Mechanical testing (tension to fracture in an Instron) revealed that "active" fibulae supported 28% more load than contralateral controls when the lateral plate was negative and the medial positive. Similarly, stiffness of the repaired fibula was greater. Histologic examination of these specimens revealed a wider "cuff" of callus (mainly fiber bone) than controls. When the positive plate was placed laterally, over the fibula, and the negative medially, strengths were 25% below control values, and larger masses of cartilage were observed in these active specimens than in their contralateral unstimulated controls. The reasons for this biologic effect are not evident at this time but may include interaction between dipoles and moving ions in tissues and the external field or interfacial charging, in a capacitor-like manner, of tissue planes in response to the field. Here, it should be noted that McElhaney and colleagues also have noted biological effects of electrostatic fields in modifying immobilization osteoporosis in rats.[33]

Although these results seemed promising, direct application to man would have posed two major problems. First, increasing the interplate distance to accomodate bulkier human extremities would require larger voltages to maintain similar field values, values already low on the basis of the tissue culture studies. Even 100-V sources attached to patients constitute a potential hazard, and larger voltages were unattractive. Second, in view of the present "state of the art," circuitry to handle a high-voltage pulsing field of this type tends to be sufficiently cumbersome to mitigate against portability. Furthermore, possible current leaks would result in major electrolysis effects. For these reasons, we decided to investigate the effects of electromagnetic fields on fracture healing in animals.

To modify artificially the electromagnetic environment of a fracture site, we coupled inductively the desired wave form. In essence, very simple and classical

means for voltage induction were employed. The principle of applying a time-varying, magnetic field to induce a time-varying voltage at right angles to the field lines is well known. In such a system, the wave form depends upon the variation in the rate of change of the magnetic field. In this manner, simple, air gap, field coils could be used with a geometry dictated by both the size of the limb and the fracture site.

The choice of induced wave form parameters was based upon the naturally occurring piezoelectric-like signal present in bone[8,24] and on tissue culture studies on fibroblasts[29] and erythrocytes.[22,34] These factors, coupled with a dynamic cellular model,[35] have allowed a time constant approach by which, possibly, a desired biological event could be selectively stimulated. In this manner, wave form amplitude, duration, and repetition rate could be chosen on a hypothetical basis. For this study, the wave form chosen is shown in FIGURE 1. It represents the signal that actually appears at the repair site under investigation. Although of shorter duration, the shape approximates that observed in deformed bone.[8,24] Hypothetically, it may be close to ideal for optimal excitation of the time constant of a given biological event[31] and can be obtained with simple, inexpensive circuitry with which the coils can be driven. By an appropriate choice of coil-driving circuit elements, two sets of wave form parameters were chosen for the majority of *in vivo* studies. The first, based upon the piezoelectric-like approach, had a peak induced voltage field at the osteotomy site of 2 mV/cm, a wave form duration of 1.5 msec, and a repetition rate of 1 Hz and is,

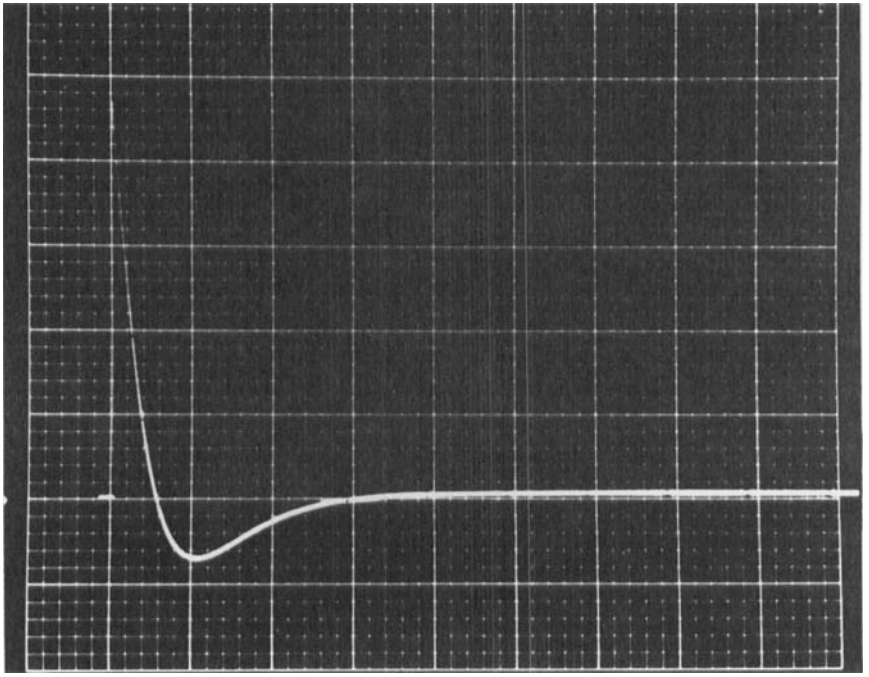

FIGURE 1. Oscilloscopic trace of magnetically induced pulse in bone with a 1-P 1-Hz circuit. The amplitude was 2 mV and pulse duration 1.5 msec. Note the biphasic character of the pulse with unequal time constants in the two phases.

herein, designated as circuit type 1-P 1-Hz. The second, which is derived from the dynamic cellular model approach, had a peak-induced voltage field of 20 mV/cm, a duration of 0.15 msec, and a repetition rate of 65 Hz and is hereafter designated as circuit type 10-P 65-Hz.

Materials and Methods

In Vitro *Determination of Optimum Coupling of Induced Wave Form*

Since the biological model chosen in this study was a fibular osteotomy in the beagle, it was decided that a grossly homogeneous voltage drop along 1.5–2 cm would be required at the fracture site. This allowed the use of rectangular coils that had internal dimensions of 2.5 × 3.0 cm. These dimensions were based upon the fact that the longest, parallel, induced voltage drop would be in a plane parallel to an inside coil edge.

To establish induced voltage field patterns in the actual model, the tibiofibular complex was removed from dogs and rabbits by disarticulation at the knee and ankle. All soft tissues were dissected subperiosteally and the samples kept moist by wetting frequently with Ringer-Tyrode's solution. Excess moisture was removed by blotting the surface of the bone prior to test. Voltages, induced in these samples, were detected by means of silver-silver chloride electrodes on the surface of the bone and by platinum-iridium electrodes inserted into the medullary cavity of the tibia. All electrodes and their leads were shielded to their tips with Conel metal to protect the wires from functioning as antennae in the electromagnetic field. To test the effectiveness of shielding, all electrodes were placed in the same spatial orientation in the field as they occupied during measurements of induced voltage in bone and were shorted. When an electrical null was obtained, the exposed tips of the electrodes were placed on the surface or into the medullary canals of the bone and the induced voltage recorded on a Tektronix 564 oscilloscope equipped with a 3A9 preamplifier. A single coil was inserted in planes parallel to the long axis of the bone and situated at various distances from it. Care was taken to position the bone as closely as possible in parallel with an inside coil edge. For these measurements, the coils were driven, with a Tacussel PIT-20-2A potentiostat, so that the induced voltage would have the shape demonstrated in FIGURE 1.

A study of the fall of induced peak voltage, as a function of distance from the plane of the coil, revealed, as expected, that only 25% of the coil voltage would be available at the fracture site if the coil were to be placed outside the skin. It was found, therefore, that an optimum arrangement was two magnetically aiding, facing coils, both of which were in identical spatial relation to the osteotomy (with respect to their position in a plane parallel to, but not necessarily equidistant from, the osteotomy). In this manner, the peak-induced voltage could be increased up to 50% of the maximum available. The geometry of the induced voltage field is well established for coils of this configuration and was verified during the course of this study by means of Hall-effect probes.

The above experiments were repeated in mature beagles, anesthetized with intravenous sodium Pentothal®. Either the tibia or femur in each of the 10 dogs was approached surgically, with care taken to use a route of exposure such that, after introduction of electrodes, overlapping tissue planes could be established over the leads. With this technique, the underlying bone never was exposed directly, through

air, to the external electromagnetic coil overlying the "operated" region. Coils were similar to those described above and were driven with the potentiostat. In this complete model, an air gap of 0.5 cm existed between the skin and coils, and the total gap between the coils was 10 cm for the femur and 7 cm for the tibia. Induced voltages in skin, muscle, and bone were recorded in a fashion similar to the above study. Identical field geometry existed, whether air, skin, or muscle was present between the plane of the coil and the bone.

In Vivo *Effect of Electromagnetic Fields on Healing of Fibular Osteotomies*

Two series of animals were studied in this phase of the experiments. Both utilized the same operative and postoperative management and analysis, except where otherwise noted. Because they varied mainly in the nature of the induced wave forms, the operative and analytical details of both series will be presented together.

A total of 41 adult, closed-colony beagles were employed in this phase of the study. Under intravenous sodium Pentothal anesthesia, a 0.5-cm skin incision was placed over both right and left fibular "heads" to permit introduction of crossed, threaded Kirschner wires to "fix" the proximal fibula to the proximal tibial metaphyses. These wires served to minimize postoperative motion of the proximal fibular segment after osteotomy. A second set of skin incisions, 0.5 cm long, was made 3.5–4.5 cm distal to the proximal fibula, in line with the right and left fibular diaphyses. The bones were exposed by separating overlying muscles along fascial planes. Care was exercised to limit soft tissue dissection to a minimum, and the periosteum was not purposefully incised at this point in the operation. A modified Love-Kerrison punch, which contained a guillotine-type end, was introduced to make the transverse osteomies. A small amount of adherent muscle and periosteum was sectioned transversely in the process. Both skin incisions on each leg were closed with sutures. At the distal end of both tibial diaphyses, two threaded Steinman pins were introduced transcutaneously, with a lateral-medial orientation, and 1.5 cm apart. These pins served to mount and stabilize two 6 × 12-cm plastic coil carriers, medial and lateral to both legs. The coil carriers were fixed to the pins by means of methylmethacrylate. Coils were mounted on the outer surfaces of the plastic with plastic screws and clips, so as to achieve the osteotomy site-coil geometry described earlier. Care was taken to assure that both coils of a pair were spatially aligned, facing one another, 6 cm apart, with the leg and its fibular osteotomy "sandwiched" between them. In this arrangement, a 0.5-cm air gap existed between the coils and the skin (FIGURE 2).

On the experimental leg, coils were coupled electrically in parallel (magnetically aiding) by an armored telephone cable to the appropriate circuits and batteries carried on the dog's back. Sixteen alkaline LeClanche "C" cells (24 V) wired in series were carried, along with the pulse-shaping circuit,* in pockets of a canvas vest worn by the dog for the duration of the experiment (FIGURE 2). The power requirements of the circuit were such that, in a 24-hr period, battery voltage decreased to approximately 18 V. The contralateral limb of each dog also carried coils, which were not powered. After operation and attachment of the devices, dogs were x-rayed to assure proper alignment of coils with the osteotomies. All animals were allowed to range freely in large cages and were fed a diet of Purina Dog Chow and canned dog

*All circuits, coils, and batteries kindly designed and supplied by ESB Company, Inc., Yardley, Pa.

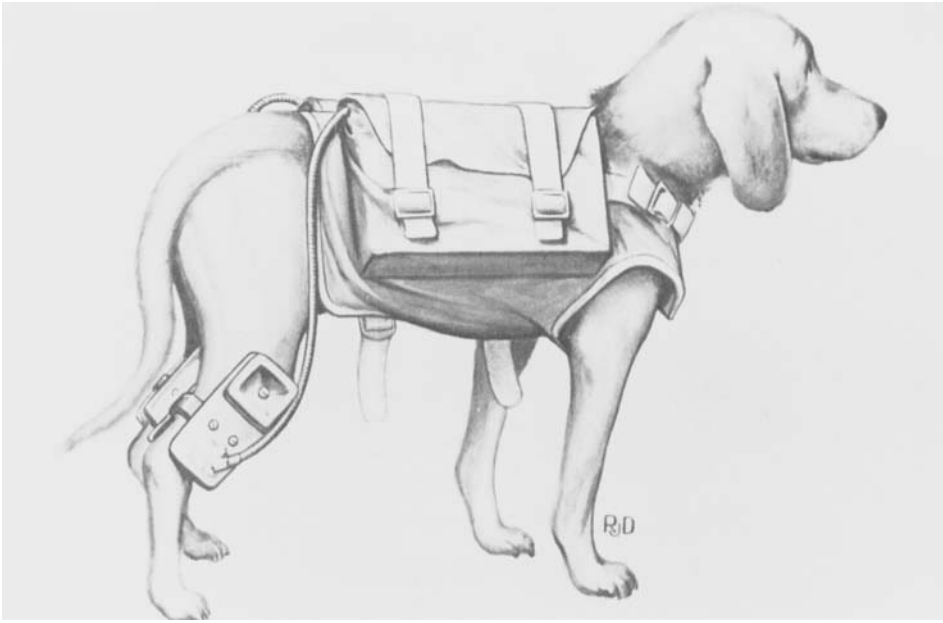

FIGURE 2. Diagram of dog with electromagnetic coils in position flanking medially and laterally the fibular osteotomies. Note the unpowered control coils on the opposite leg. Vest carries batteries (24 V) and pulse-shaping circuits.

food. Circuits were checked daily for proper operation, at the time of battery change, every 24 hr during the experiment.

Animals were sacrificed on the 28th postoperative day. After removal of equipment, the legs were severed at the knees and ankles. Soft tissues were stripped from the fibulae, taking care to preserve the callus intact during dissection and separation from the tibia. Specimens were x-rayed in anteroposterior and lateral projections on industrial grade film.

Mechanical testing of callus stiffness and viscoelastic behavior was conducted on wet specimens promptly after radiography. The proximal end of each fibula was embedded in a cylindrical mass of methylmethacrylate. When fully polymerized, the plastic cylinder, which contained the exposed osteotomy and distal fibula, was mounted in a clamp as a cantilever (FIGURE 3). Specimens were deformed through fixed distances of 0.025, 0.050, and 0.075 in. by a plunger at the distal end of the specimen. The loads required to produce these deformations were recorded from a Bytrex JP-25 load cell, coupled to a Tektronix 5103N-D13 storage beam oscilloscope, over an interval of 100 sec after the onset of rapid loading. Each specimen was tested in five rotational positions at each level of deformation, namely, anteroposterior (0°), lateral-medial (90°), postero-anterior (180°), medial-lateral (270°), and, finally, anteroposterior (0°). Sufficient time was permitted to elapse to allow for viscoelastic effects to dissipate between deformations, and the effectiveness of this step was monitored by comparing load values at the onset of testing (0°) with that at the completion of testing (0°).

When mechanical studies were completed on a pair of fibulae, they were fixed in

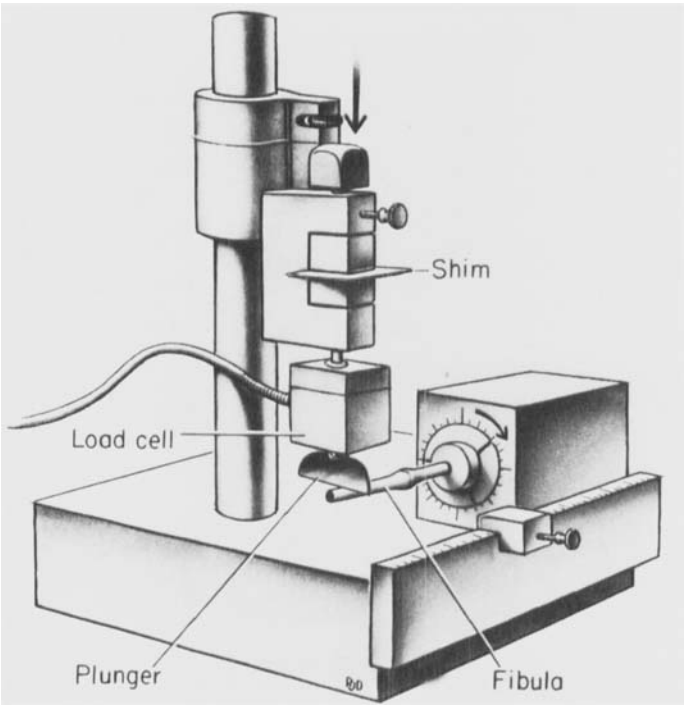

FIGURE 3. Diagram of mechanical testing device. Note the specimen mounted in the methylmethacrylate cylinder, which can be rotated to position fibula in the antero-posterior (0°), medial-lateral (90°), postero-anterior (180°), and lateral-medial (270°) orientations with respect to the plunger-tipped load cell. The deformations of 0.025, 0.050, and 0.075 in. were determined by shim thickness. A fixed lever arm distance and osteotomy to mounting block distance were used for all specimens.

formol-saline, decalcified in 10% formic acid, embedded in paraffin, and sectioned serially in the long axis of the specimen. Selected paraffin sections were stained with hematoxylin and eosin. Microscopic analysis of this material, in addition to evaluation of radiographic and mechanical testing data, was performed by observers with no initial knowledge of specimen origin.

As noted previously in this section, two series of animals were studied, utilizing the basic design given above. In the first of these, the effects of the 1-P 1-Hz wave form were investigated. The second series of animals were stimulated with the 10-P 65-Hz wave form.

RESULTS

In Vitro

Precise mapping of the induced voltage field was performed in air, denuded bone, and on whole limbs. The parameters measured were loss in induced peak voltage

drop as a function of distance from the coil, the level of induced voltage at positions outside the coil dimensions, and the shape of the induced voltage in various tissues.

For any tissue position, relative to the coil, the induced voltage wave form was identical to that shown in FIGURE 1, which indicated no bulk rectification or capacitive effects. The level of induced voltage at the osteotomy site when two magnetically aiding coils were employed was 2 mV/cm for the 1-P 1-Hz circuits and 20 mV/cm for the 10-P 65-Hz circuits. Finally, the field mapping showed that, at a position 2 mm from the center of the outer edge of the coil, the induced voltage falls to 1% of its maximum value. In all phases of this *in vitro* study, the results indicated a critical spatial relationship between coils, tissues, and induced voltage drops. No significant temperature variations were detected in tissues within the fields. In view of the average power levels achieved by these circuits ($\approx 10^{-4}$ W/cm^2 of tissue area), joule heating is largely precluded.

In Vivo

1-P 1-Hz

In the first series of experiments (1-P 1-Hz circuits), 20 of 22 animals were available for study after 28 days. Two dogs were eliminated from the investigation because of intercurrent infection and equipment failure. In 10 animals, the stimulated leg produced larger load values than the contralateral control. An equal number of animals had the greater load value associated with the unstimulated side when right and left fibulae from the same animal were compared. These results were obtained in the following manner. An average of the sums of the four load values in each specimen orientation (0, 90, 180, and 270°), at one second, was computed for each deformation (0.025, 0.050, and 0.075 in.) for both the stimulated and unstimulated control fibulae. The average value for each of a pair was expressed as a percentage, with the lower value fixed at 100%. The average of the accumulative value for the percentages in the 10 animals with the stimulated leg stiffer than its control was 260%. In the 10 animals with control legs that tested stiffer than the contralateral stimulated leg, the average of the accumulative value was 70%. The mean load values given in TABLE I, however, reveal no statistically significant difference between stimulated (actives) and their controls.

Radiographic examination revealed a wide range of healing patterns, from a small callus and evidence of early bridging of the "osteotomy" gap to a bulky callus with the appearance of an "incipient" pseudoarthrosis. Interestingly, the x-ray ap-

TABLE I

CANTILEVER LOAD VALUES* FOR THE 20 1-P 1-HZ ANIMALS

Deformation (in.)	"Active" Load (g) $\bar{x} \pm S\bar{x}$	Control Load (g) $\bar{x} \pm S\bar{x}$	Significance†
0.025	25.3 ± 5.2	22.5 ± 4.7	NS‡
0.050	59.2 ± 11.2	49.9 ± 10.3	NS
0.075	86.9 ± 17.4	85.1 ± 19.9	NS

*Measured in grams at 1 sec. Mean of the sum of average loads at approximately 0, 90, 180, and 270°.

†Students paired difference *t* test.

‡Not significant.

pearance of the specimen could be correlated with the mechanical testing behavior in a large majority of the specimens.

Histologic patterns could be correlated generally with the radiographic appearance of a specimen but were less reliable in predicting mechanical behavior. A circumferential callus was present in all specimens but varied greatly in bulk. In general, animals that demonstrated the greatest stiffness on mechanical testing presented the smallest mass of external callus on histologic examination (FIGURE 4). Specimens of this type occasionally had fibrocartilage linking the ends of the cortex, without evidence of a cleft. Unlike stiffer specimens, those with low load values possessed the largest bulk of external callus (FIGURE 5). Proximally and distally on the fibular diaphysis, a fiber bone pattern predominated. Near the osteotomy, large masses of cartilage (both hyaline and fibrocartilage) were customary. Frequently, a transverse cleft could be seen extending from the osteotomy radially through the external callus. In these specimens, patterns suggestive of endochondral ossification were rarely seen, and there was extensive osteoclastic resorption of the bone fragments proximal and distal to the osteotomy. With the exception of variations in the bulk of the callus present, no differences in spatial orientation of reparative tissues were observed in aligned specimens. When the fragments were off axis in any plane, however, the surfaces of the proximal and distal diaphyses toward the direction of the shift were characterized by advanced osteoclastic resorption. In such specimens, callus formation was scanty on these surfaces, except at the exact level of the osteotomy. On the surfaces away from the shift, large masses of callus were observed.

The histologic features of the repair process in the magnetically stimulated fibulae were identical to those of the unstimulated controls. In no section was there any evidence of tissues with malignant or premalignant changes. Mitoses were uncommon. The surrounding soft tissues, including muscle and vessels, were entirely normal. When these tissues were surgically uninvolved, there was no evidence of repair, cell proliferation, or increased extracellular matrix. It was impossible in these specimens to determine whether there was an alteration in the extent or orientation of the vascular bed in response to stimulation.

10-P 65-Hz

The second series contained 15 animals with 10-P 65-Hz circuits. A total of 13 dogs were available for study at the end of 28 days; two of the animals had been eliminated previously because of infection or circuit abnormalities. In 10 of the 13 animals, the stimulated leg produced larger load values than the contralateral control. Three animals had the greater load value associated with the control leg. This finding is significant at $p < 0.07$ by the sign test. These results were obtained on the basis of an analysis of 1-sec load values, listed in TABLE 1 for the 1-P 1-Hz animals. The average of the accumulated percentage values for the 10 animals is 89%, and 40% for the three animals in which the control leg gave larger loads than the stimulated counterpart. TABLE 2 presents the mean load values and the standard errors. It can be seen that, at each deformation, the active values are statistically significant when compared with controls. As the larger deformations are reached, however, there is a greater range of variable results, and at 0.050 and 0.075 in., the populations of values are skewed.

Radiographic and histologic results were similar to those described for the 1-P 1-Hz series, with several important exceptions. First, high or low load values could be predicted from either method of analysis in the large majority of the specimens

FIGURE 4. Hematoxylin and eosin longitudinal specimen of a 1-P 1-Hz stimulated fibula. This animal had a large load value and demonstrates a medium to small callus, with partial cleft healing and a minimum of cartilage. × 10.

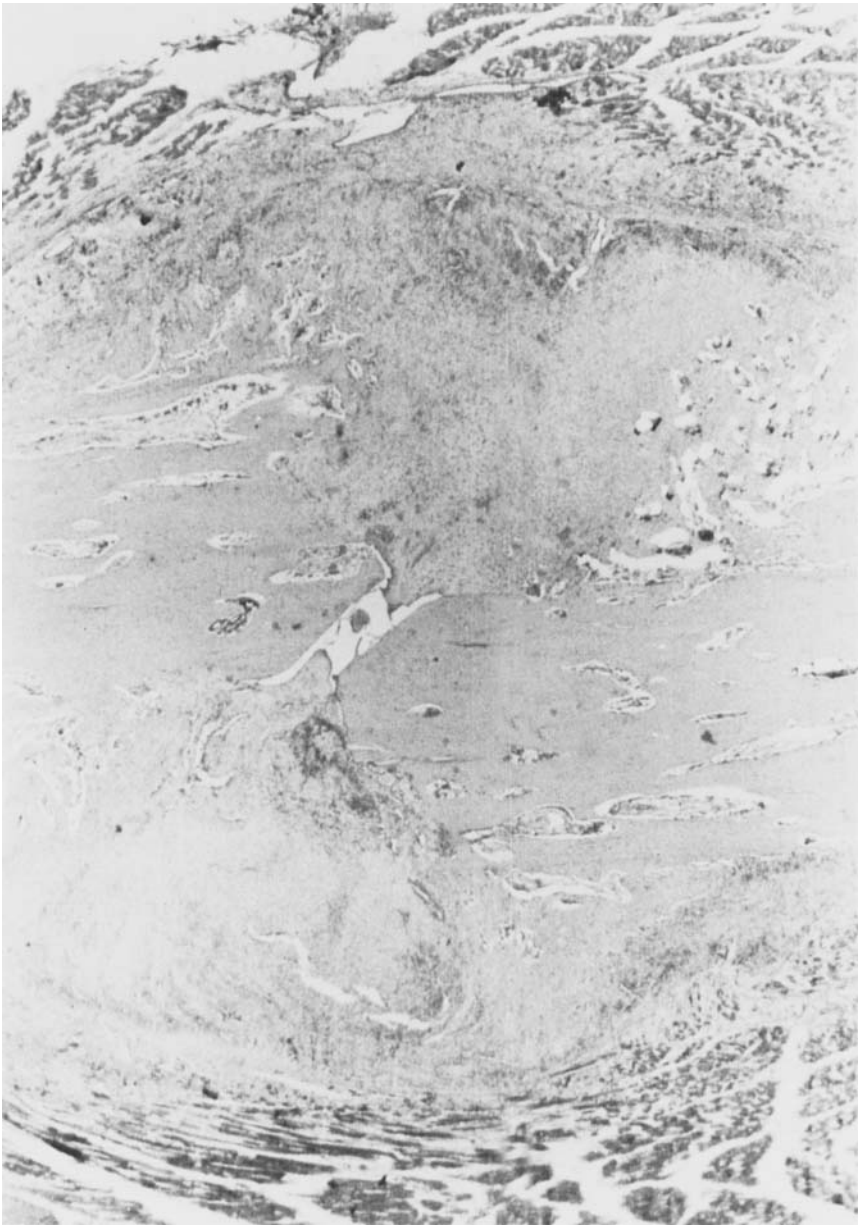

FIGURE 5. Hematoxylin and eosin longitudinal specimen of a 1-P 1-Hz nonstimulated control fibula. Note the larger callus bulk than that seen in FIGURE 5. A large amount of cartilage was present in this fibula, which gave low load values. × 10.

TABLE 2

CANTILEVER LOAD VALUES* IN THE 13 10-P 65-Hz ANIMALS

Deformation (in.)	"Active" Load (g) $\bar{x} \pm S\bar{x}$	Control Load (g) $\bar{x} \pm S\bar{x}$	Distribution	Significance†
0.025	28.2 ± 4.6	19.8 ± 4.3	Normal	<.05
0.050	63.5 ± 10.4	41.2 ± 8.5	Skewed	<.05
0.075	134.5 ± 42.6	63.2 ± 13.1	Skewed	<.10

*Measured in grams at 1 sec. Mean of the sum of average loads at approximately 0, 90, 180, and 270°.

†Student's paired different *t* test.

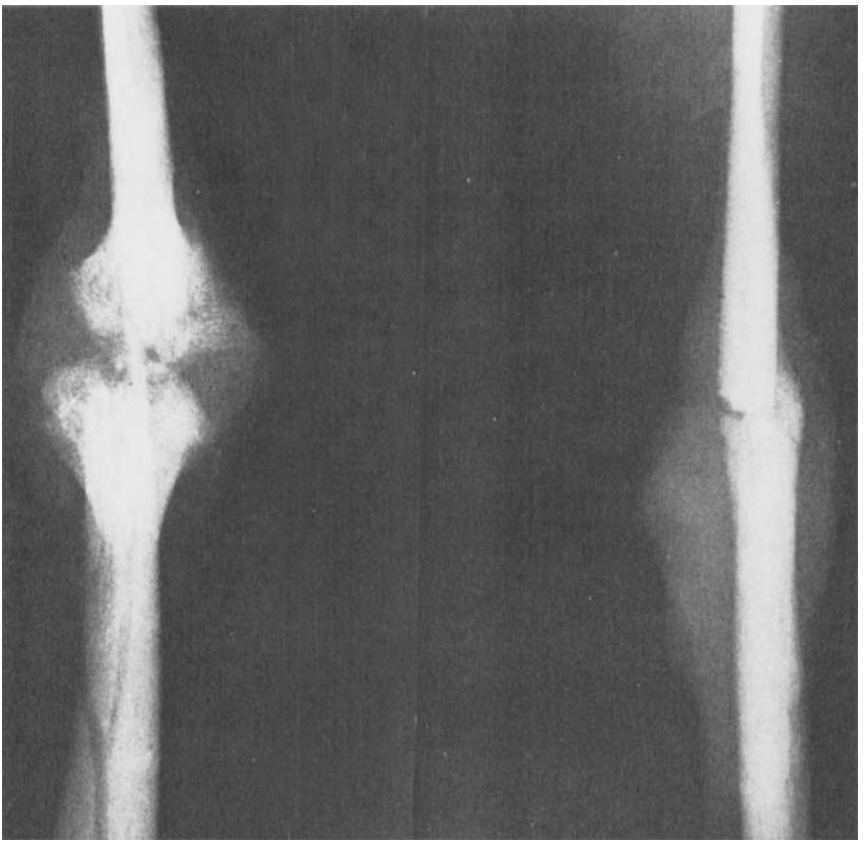

FIGURE 6. (*Left*) Radiograph of control fibula from a 10-P 65-Hz animal after 28 days. Note the large callus and "incipient" pseudoarthrosis. This specimen exhibited low values on mechanical testing. (*Right*) Contralateral fibula stimulated with 10-P 65-Hz for 28 days. Note the small callus and early bridging. This specimen displayed large load values on mechanical testing.

(FIGURE 6). Second, the stimulated legs demonstrated continuous bony union with fiber bone in 7 of 10 actives and a very small bulk of callus, which was generally smaller than that depicted in FIGURE 4. Here, it should be noted that the three control specimens that tested higher than their active counterparts failed to display this pattern. Furthermore, in 5 of 10 actives, unlike the controls (FIGURE 7), the bone ends were linked with bundles of fibroosseous tissue, which were aligned generally parallel to the long axis of the bone (FIGURE 8). In these, the gap, present between the cortical ends that flanked the osteotomy site, was partially to totally filled with fibroosseous tissue. This situation was only occasionally observed in the 1-P 1-Hz active or 10-P 65-Hz control (unstimulated) specimens. Extensive osteoclasia of the cortical margins at the gap, also, rarely was observed in these sections. Conversely, the ends of the cortical bone in the gap region frequently were covered with lamellar-type bone. Unlike control specimens, when chondroid material or cartilage was present, it appeared to be eroded extensively by vessels in an endochondral-type ossification. Again, all tissues were characterized by a pattern that was normal for the amount of trauma to bone and soft parts. In none of the stimulated specimens was there any evidence of neoplastic or preneoplastic processes.

DISCUSSION

Many, if not all, biologic systems are affected by electromagnetic radiation. In the major portion of the electromagnetic spectrum, the effects are nonthermal in

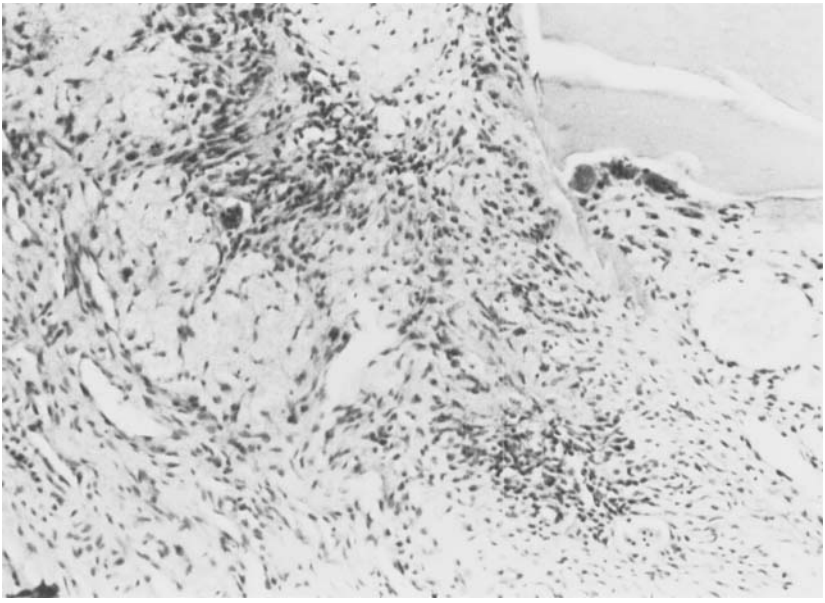

FIGURE 7. Hematoxylin and eosin longitudinal specimen of a 10-P 65-Hz control fibula. Note the distal cortical fragment (*upper right*). The gap region (*left*) is filled with fibrous tissue that has no preferred orientation. Little or no osteogenesis on "fracture" margins are evident. × 40.

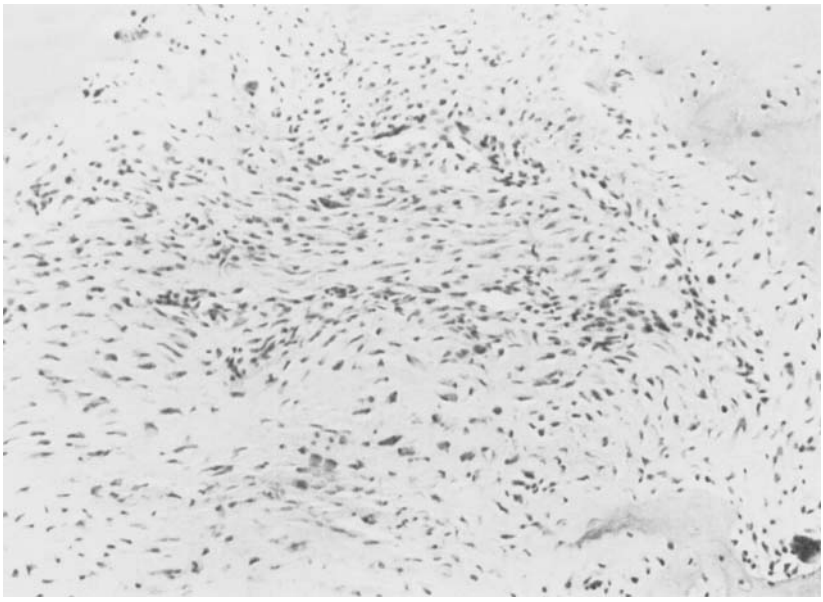

FIGURE 8. Hematoxylin and eosin longitudinal specimen of a 10-P 65-Hz stimulated fibula. Note osteogenesis on the ends of the "fractured" fibula (*upper right* and *left*). The fibroosseous tissue in the gap region has a preferred longitudinal orientation. Compare this photomicrograph with FIGURE 7. × 40.

origin. This is certainly so at the low primary frequencies and energy input utilized here. Because it is not the purpose of this article to document the range of observations, the extensive reviews of this topic by Presman[36] and by Marha and colleagues[37] are recommended. Furthermore, no attempt will be made here to speculate on the actual mechanisms by which the electromagnetic fields are capable of producing the several results described in this article. Some of these have been reviewed briefly in the introduction and elsewhere.[1,7,38]

This preliminary study indicates that low-frequency electromagnetic fields of low intensity applied across an extremity will induce voltages of a magnitude generally produced by deformation.[8,24–27] These voltages, which may well have biologic significance, range from 0.1 to 50 mV/cm in bone and higher in soft tissues because of their closer proximity to the coil. The induced voltage apparently is capable of altering the rate and pattern of bone healing in dogs, so as to increase the stiffness of the reparative tissues to a significant extent at 28 days after osteotomy (fracture). The results seem to parallel to a major degree the observations that stimulation of fracture healing in man[21,39–41] and animals[13–16,18–20,42] can be accomplished by artificial electrical currents. Here, it should be noted that the choice of the wave form to achieve these results was based on a rational approach, which centered on the specificty of electrical time constants. These are described elsewhere.[31]

To the authors' knowledge, this is the first report that pulsed electromagnetic fields, which originated from points outside the body, can accelerate repair processes. The essential differences between the present studies and those reported by Kraus and Lechner[21] should be noted. Although these latter investigators used

coils driven with ac signals outside the skin to affect the repair of fractures and pseudoarthroses, their external coils are only a part of a more complex implanted system, which requires a secondary element (induction coil) attached to electrodes (screws and nails) that are implanted surgically in the patient. Their system, therefore, is more similar to the dc stimuli cited in the introduction than to the present system. In other words, the Kraus and Lechner method, although effective in clinical application, is surgically invasive and substitutes an implanted induction coil for the usual batteries to power the electrodes. Here, it should be emphasized that the Steinman pins and Kirschner wires implanted in the present experiment serve only a mechanical purpose (to "fix" the apparatus and "fracture" site) and are situated outside the effective electromagnetic field. In human applications, pins probably will not be required, because the plaster cast itself can be used to mount the equipment.

Once osteotomized, the dog's fibula is considerably mobile, and a significant range of motion between fragments occurs during function. With the intact tibia to hold the fibular ends apart, this system might well be expected to develop delayed unions or frank pseudoarthoses. In fact, in a series of control animals without coils on either leg, this type of osteotomy resulted in a pseudarthosis pattern of repair in 50% of the extremities observed for periods longer than 28 days (2–6 months). Attempts to improve the stability of the system with crossed Kirschner wires through the fibular head into the tibia were only partly successful. Radiographic and histologic data attest to the contention that a significant amount of motion of the bone ends occurred throughout the healing period, in most animals. In fact, the clinical and experimental observations noted by others[43] that the bulk of a callus is related directly to the amount of motion at the fracture site seemed to have its counterpart in the present experiments. It is all the more encouraging, therefore, that electromagnetic stimulation was able to overcome these adverse experimental conditions to produce early bony union in the majority of animals at 28 days.

Specimens in the 10-P 65-Hz series, which gave high load values, were characterized not only by a small mass of callus but also by fibroosseous or osseous tissue that united the osteotomized ends of the fibula. Furthermore, there was a striking longitudinal orientation of the newly formed tissue in the gap in the stimulated legs in which bridging had occurred. When cartilage was present in the callus of "active" specimens, unlike the controls, it usually displayed advanced endochondral-like ossification. It would seem, therefore, that the major effects of electromagnetic field stimulation were exerted on architectural and maturation aspects of the reparative process; that is, the healing process was accelerated. An interesting phase of this study, in which ^{45}Ca was injected into the animals at five intervals before sacrifice, will be reported elsewhere. The results, however, indicated that uptake in the active limbs was decreased and, in many animals, was less than control limb values. In fact, there appeared to be an inverse relationship between ^{45}Ca uptake and stiffness. This finding, coupled with the differences in callus bulk, suggests further that one explanation for the results may be an increased rate of spatial and tissue maturation in the stimulated animals. The findings do favor the view that these aspects may have helped to control motion and, thereby, exercised a salutory effect on bone briding. At the present time, it is not known to what degree such factors as increased collagen synthesis, dipole orientation, and magnethohydrodynamic pumping in vessels and nerves are responsible for these results.

Before leaving this phase of the discussion, it would seem important to reemphasize that the improved results in stimulated animals did not derive from an increased mass of cells. Fear has been expressed by some investigators in this area

that electrical stimulation by fields and currents may result in cancer, possibly through a general enhancement of growth. No evidence of such effects was present in these experiments. Quite to the contrary, the reparative tissue in the stimulated specimens, generally, was less cellular than the controls. None of the histologic material revealed any evidence of neoplastic changes. It would appear from these observations that the low frequencies and field strengths are reasonably safe when considered from the "carcinogenic" standpoint. This statement is made, however, with the realization that long-term observations, in larger groups of animals, will be required before categoric pronouncements can be made. Should the lack of malignant alterations prove insufficient testimony to the short-term safety of this method, it should be remembered that Humphrey and Seale reported in 1959[44] the use of direct currents to retard tumor growth in experimental animals. Similar results have been observed in these laboratories.[45] Recently, the induced wave form used in the present investigations (10-P 65-Hz) has been employed in a preliminary study of the electromagnetic field effects on the behavior of Meth A sarcomas in Balb/C mice. Not only was the mortality rate reduced from 80% in the controls to zero in the field-exposed mice, but marked inhibition of tumor growth was observed in experimental animals over the 10-day observation period.[45]

The results of these studies indicate that the present 10-P 65-Hz induced wave form with associated circuitry may be sufficiently practical, safe, and efficacious to justify controlled application of the method to human fractures and pseudarthroses. Obviously, much additional laboratory investigation must parallel the studies in man. There is a need to define long-term effects, clarify mechanisms, improve technology, and delineate the scope of usefulness of electromagnetic fields as a therapeutic modality. If fracture healing can be accelerated, it would seem likely that many other regenerative and reparative processes, such as wound healing and neural regeneration, also may be influenced.

Although outside the scope of formal discussion of results, it seems pertinent to raise one further issue. The general scientific and medical communities may be unprepared to meet the challenge of the future if the principles being enunciated here bear fruit and "electrotherapy" takes its place in the therapeutic armamentarium. Unfortunately, prejudice born of broken promises by charlatans with "little black electrical boxes" and a lack of "hard" data has closed to all but a few minds the "potentials" of manipulating internal and external electrical and magnetic environments for the benefit of mankind. If, as seems possible, this type of research continues to mushroom, within the next two decades, methods of electrical treatment may become available to physicians ill-equipped by training to apply them. No one would argue that a medical practitioner should understand the principles of pharmacology before prescribing drugs. Where, therefore, will the physician of the future be with little or no working knowledge of biophysics, bioelectrochemistry, and electronics? Is it too early to reexamine medical school curriculae with these possibilities in mind? Hopefully, we will be able to deal equally effectively with the specific issues of scientific endeavor and the broader issue of their pertinence to society.

Acknowledgments

The authors appreciate the expert technical assistance of Mr. Eleut Hernandez and Mr. Michael Manning.

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DISCUSSION

DR. Z. B. FRIEDENBERG: Did you notice any change in the bone distal to the side of the fracture? In other words, were all of your effects confined to the area of the fracture? What about the joint, the adjacent tibia, and the rest of the fibula?

DR. BASSETT: You mean in the fields?

DR. FRIEDENBERG: Yes.

DR. BASSETT: Thus far, we have seen no changes in the cortical bone, and we

have not looked at the adjacent tibia and have certainly not looked at the joints. I should point out, however, that this field pattern is highly specific, and with our coils, the effective field is confined to the central area between the coils; the coil geometry is such that the field drops off exponentially outside of it. I therefore think we have very little or no effective field outside the central area between the coils, so we can actually direct the therapeutic modality in this way.

DR. FRIEDENBERG: Have you tried it on intact bone?

DR. BASSETT: No, but we have tried it on control bone. These are preliminary presentations, and obviously there is still much work to be done.

DR. H. M. SHAPIRO (*G. D. Searle & Co., Chicago, Ill.*): I think this work is very exciting, and I am amazed by the progress that has been made in this area. But, I think with regard to your discussion about neoplasia, it should be pointed out that, except surgery, most of the therapeutic modalities currently used to treat neoplastic disease also have a potential for inducing it. For example, although x-rays at first will shrink many tumors, in the long run, they will also induce some of them. This indicates that although pulsed fields may eventually be a good technique for treating tumors, when used for about 10 days, several months will probably have to elapse before confirming its effectiveness.

DR. BASSETT: I agree; I tried to emphasize that these presentations are very preliminary. They were only provided to show that there is activity in another biologic system. It will be a long time until we have some clinical studies to back them up.

DR. D. D. LEVY: Dr. Bassett, what did the notations one power and ten power refer to in your Figure? Also, how long did it take to effect the state of repair that your Figure had indicated for the active in the control?

DR. BASSETT: Twenty-eight days was the observation period, and I will discuss the power notations later, because they are highly complex. Essentially, we are dealing with a 24-V peak-to-peak signal; I can give you the other parameters later.