SECTION III

BASIC SCIENCE AND PATHOLOGY

The Significance of Electrically Stimulated Osteogenesis

More Questions Than Answers

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While the present technique of electrical osteogenesis appears to be the latest application of modern technology, its roots go back to the beginning of the scientific revolution. In 1600 William Gilbert, physician to Queen Elizabeth, published his book "De Magnetic," in which he clearly differentiated for the first time between electrical force and magnetic force.[21] Perhaps more importantly, he advocated for the first time, "trustworthy experiments" as opposed to "probable guesses and opinions." At that time and for the next 200 years, the concept of how living things worked was dominated by "humors," fluids with various mystical and mechanical properties. Despite "trustworthy experiments" of such workers as Hale,[22] this concept was vigorously defended against suggestions that Gilbert's electrical forces might be involved in living things until Galvani published his "Commentaries".[19] In this, he reported a number of observations clearly relating electricity to the nerve muscle preparation which he interpreted as evidence for intrinsic "animal electricity." This concept became identified as "vitalism" as opposed to "mechanism" espoused chiefly by Volta.[36] A scientific debate of classical proportions developed until 1848, when du Bois-Reymond described the nerve impulse and correctly ascribed it to something other than the flow of electricity along the nerve.[16] du Bois-Reymond's pupil Bernstein proposed a traveling wave of depolarization in the nerve membrane in 1868.[13] This "Bernstein hypothesis" has survived virtually intact until the present time and has dominated scientific thinking to the virtual exclusion of all others. Today the physiology texts recognize the current of injury as the last remaining vestige of Galvani's vitalism, but dismiss it as a second order phenomenon of no biological significance.

Throughout this period of intense debate on animal electricity and vitalism, clinicians of all sorts were enthusiastically applying the novel "Galvanic" (DC) and "Faradic" (AC) currents to a wide variety of patients. In a monograph on pseudarthrosis by Hartshorne written in 1841, the author refers to the treatment of a tibial non-union in 1812 with "shocks of electric" fluid by a Mr. Birch, "surgeon at St. Thomas' Hospital."[23] By 1861 the technique had progressed to the point that Dr. Arthur Garrett, a fellow of the Massachusetts Medical

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Society, published a compendium of electrophysiology and electrotherapeutics dealing with a wide variety of clinical conditions.[20] His treatment for pseudoarthroses was the application of direct current through gold needles, insulated except at the tips which were inserted into the site. According to Garrett, this treatment never failed him! Thus we see the classical conflict between the dogmatist who insists that something cannot be and the experimentalist who insists he saw it. Resolution was not to come until the early years of the 20th century when the last remaining problem with the Bernstein hypothesis, conduction across the synapse, was solved by Otto Loewi's demonstration of acetyl choline.[25] The only remaining electrical phenomena in living things was the polarized membrane resulting from ion selectivity and all therapeutic uses of electrical current were without foundation. At about the same time the Flexner report resulted in a revolutionary change in the organization of medicine; quackery (such as electrotherapeutics) was vigorously dealt with and the rule of science over art established. All life was viewed as "chemical clockwork," complicated perhaps, but understandable in technological terms. Now, 50 years later, we find persistent and ever more numerous reports in the clinical literature claiming the stimulation of osteogenesis by voltages, currents or fields that the body of science knows can have no physiological effect. Aside from the obvious question of clinical merit, a more fundamental question arises; is this simply a return to pseudoscientific quackery or is it finally a serious challenge to the mechanistic concept? The questions are decidedly nontrivial, for if electrical osteogenesis is real, it represents the first time in the history of medicine that the clinician has been given the power to initiate growth of any tissue on command. The deliberations on this topic carry implications for all of medicine and it is the responsibility of orthopedics to now proceed in a fashion consistent with the principles laid down by Gilbert in 1600.

MODERN DEVELOPMENTS

In the years between 1910 and 1950, little scientific attention was directed towards bioelectric phenomena and that which was done, such as by Burr[15] and Barth,[1] was largely ignored. However, during the same period much progress was made in our knowledge of electricity, culminating in the establishment of electronics, cybenetics and solid state physics as recognized disciplines. The importance of these developments was the demonstration that, in the physical world at least, very small currents and voltages were capable of profound effects. It must be remembered that man's use of electricity from 1880 to until the invention of the vacuum tube by DeForest in 1907 was limited to power concepts requiring large currents and high voltages. DeForest established *electronics* dealing with millivolts and microamperes as opposed to *electrical* dealing with voltages and currents thousands of times greater. A similar turning point in biology was established in 1939 by Szent-Gyorgyi who proposed that solid state electronic mechanisms were physiologically significant.[34]

In 1953 Yasuda reported on the presence of one such property, piezoelectricity (generation of electrical potentials by mechanical stress) in bone.[37] He proposed that these stress generated potentials were the primary cause of the bone growth resulting from such stress and was able to demonstrate that 1 μA of continuous current, administered for three weeks, produced new bone growth in rabbit femora. However, Yasuda's piezoelectricity was based upon a property unique to the ultrastructure of bone and therefore not a general biological phenomenon. Since Yasuda's original report, bone has been reported to have pyroelectric,[24] semoconduction[8] and electret[27] properties, all based upon the precise organization of the hard matrix.

In 1961 Becker reported correlations between limb regeneration and certain specific properties of the current of injury in the salamander.[6] He noted similar electrical potential changes over long bone fractures in the same species and proposed a neural origin for the current of injury, postulating that it represented a general healing mechanism. Subsequently, Bassett and Becker reported stress-generated voltages in bone, which appeared to be partially related to a piezoelectric property, but which required an additional mechanism.[2] The classical piezoelectrical material produces a single pulse of one polarity on deformation and an equal pulse of opposite polarity on the release from deforming force with no continuous flow of current at any time. Bassett and Becker observed a partial rectification process which resulted in an unbalanced signal producing a net transfer of electricity in one direction. By 1964 Becker, Bassett and Bachman had refined their model, indicated its relationship to Wolff's law and demonstrated the necessary rectification property.[7] The latter was ascribed to semiconduction properties of bone collagen and bone mineral, producing a specific device, the PN junction diode, at their interface.

This rectification resulted in areas of compression stress having a net overall charge negative in polarity, while areas of tension were positively charged. On this basis Bassett, Pawluk and Becker implanted DC devices in dog femora terminating in electrodes of negative and positive polarity penetrating the medullary cavity.[3] New bone growth occurred in the vicinity of the negative electrode and not around the positive electrode. Their devices, in common with Yasuda's, produced continuous or DC current and did not simulate the impulses that would result from the operation of the piezoelectric system. While electrical osteogenesis was demonstrated, it had no relationship to the piezoelectric mechanism other than a polarity separation. In 1966, Friedenberg and Brighton reported that fractures of mammalian long bones demonstrated electronegativity similar to that previously reported in salamander limb regeneration and fracture healing by Becker.[17] Becker continued to evaluate bioelectric phenomena associated with healing in general and by 1966 believed he had identified them as an organized property of the nervous system. In the following year Smith reported the stimulation of partial limb regeneration in the frog by simulating the electrical potentials in the salamander.[32] Finally, in 1970, Becker and Murray described the electrical control system stimulating and regulating fracture healing in the amphibia.[9] In this paper they demonstrated the neural relationship of the potentials and most significantly, accurately measured the electrical current producing the primary cellular changes associated with the fracture healing. Based upon this work, Becker and Spadaro were subsequently able to demonstrate the stimulation of partial limb regeneration in the mammal by the application of similar levels of current and voltage.[10]

In 1971 Friedenberg reported the first modern clinical application.[18] He succeeded in producing healing of a non-union of the medial malleolus by the passage of 10 μA DC through stainless steel electrodes with the cathode at the fracture site. Following Friedenberg's demonstration, a number of other investigators began clinical experimentation utilizing a variety of techniques. Present clinical reports are numerous and electrical osteogenesis has recently been the subject of a special volume of this journal. Spadaro reviewed the literature, finding 42 animal studies, 25 human studies and 6 *in vitro* cell/organ culture reports.[33] He collected a total of 119 literature reports including theoretical papers, historical reviews and patent applications, with an almost exponential increase in numbers published per year starting in 1966. The bulk of the reports indicated stimulation of bone growth with a variety of electrical techniques, only 6 reports containing negative or equivocal results. In view of the di-

versity of techniques applied, he speculated that the reports represented a class of responses with separate mechanisms of action, as yet unidentified. Unfortunately this situation remains unchanged at this writing.

It is not the purpose of this paper to review in detail all of the techniques currently in use; an adequate forum for this purpose having been provided by the special volume of this journal in 1977 (Vol. 124). Instead I will attempt to simplify the various aspects, particularly those in common, speculate upon possible mechanisms of action, emphasize the questions raised and suggest those areas requiring systematic investigation.

With few exceptions, all techniques involve the insertion of electrodes, albeit of various types, into the marrow cavity of the long bones. Again, with the exception of congenital pseudarthrosis of the tibia, most techniques involve non-unions of fractures of the long bones, and finally most techniques utilize direct currents of various amounts, with the cathode being considered the stimulatory electrode. All of these technical factors are remarkedly similar to those utilized by Garrett in 1860.[20] If the present techniques are not to suffer the same fate as those of 1860, they must be based upon a firmer theoretical framework, capable of being scientifically evaluated and proven biologically active. It is the author's contention that such a theoretical framework exists based upon our present knowledge of growth control systems in general and bone growth in specific.

The phenomenon of healing is evidenced by all animals although to varying degrees of competency. The lower animals possess amazing capacity for regeneration, the replacement of body parts lost due to trauma by a specific highly competent growth process. Ascending the phylogenetic scale, the highest animals demonstrating this to any extent are the tailed amphibia. Beyond this group, regenerative ability declines sharply until in the mammalia, it is limited in the adult to the endosteal or marrow component of fracture healing (a few tissues with a normally high mitotic index, such as skin, liver and gut demonstrate regrowth, but it is based upon a higher mitotic index and lacks most of the features associated with true regeneration). In a series of papers in the 50's, Singer demonstrated that the essential element in all regenerative growth is the presence of a "threshold" mass of nerve tissue at the site.[31] The factor supplied by this tissue was unknown until the experimental evidences obtained over the past 20 years indicated that it was a negative electrical environment resulting from the flow of a continuous electrical current. While several studies have indicated that animals not normally capable of regeneration could be induced to do so by direct current cathodal stimulation, the final identification of this as the neural factor was only recently made by Rose who obtained regeneration in denervated salamander extremities by applying the proper current levels and polarity.[30] Thus one can now construct a control system stimulating and regulating regeneration in general and fracture healing in man, based upon these concepts (Fig. 1).

Several correlations are apparent from such an analysis. First, the essential role played by the central nervous system which is substantiated by common clinical experience. Secondly, the concept requires that the central nervous system or some element thereof, contains a second data control system, electronic in nature, more primitive and basic to the well known action potential. While this appears at first glance to be heretical, a surprising amount of support can be mustered for it from various disciplines.[11,12] Thirdly, and most important for this discussion, the final portion of the control loop involves the living cells. Without an adequate cell population capable of being "turned on" by the stimulus, growth and healing cannot occur. With all the interest in the various solid state properties of the bone matrix, this fact seems to have been forgotten. While such properties no doubt do exist

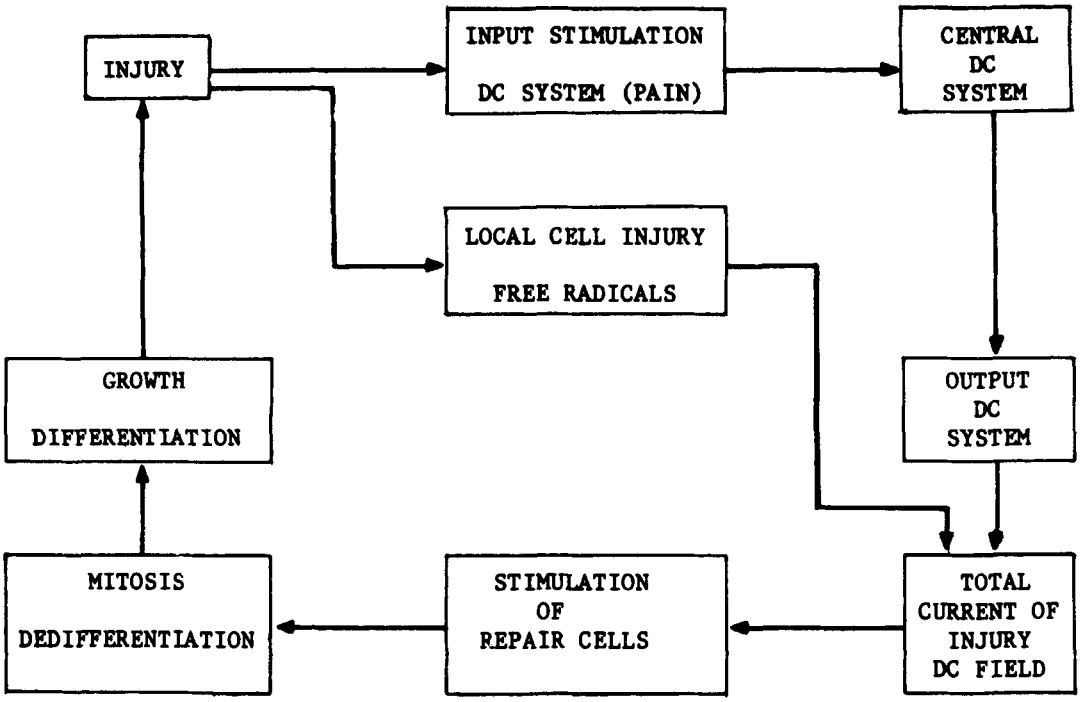

FIG. 1. Postulated control system stimulating healing. It is believed that this system operates to produce the healing of all injuries including bone repair. The injury results in some local factors, notably free radicals and activates the DC system which is part of the CNS. These two factors combine to produce an electrical environment at the site of injury which is stimulatory to the reparative cells. Obviously, the action of the system may be simulated by artificially producing a similar electrical environment.

and most likely serve some physiological function, this function must be expressed by living cells through some linkage with the matrix physical properties. The concept further provides us with a useful frame of reference for understanding the basic causes of clinical non-union of fractures. All available evidence indicates that once the regenerative control system is triggered into action by trauma, it proceeds in a self limited fashion, with the cell stimulating signal gradually declining until the system shuts down at a predictable time. By the time the system has ceased acting, the salamander should have regenerated his limb and man should have healed his fracture. Therefore, except for such conditions as neurological disturbances, vascular insufficiency or severe nutritional deficiencies, all simple fractures should heal, provided they are adequately reduced, immobilized and approximated so that the cellular activities at each end may come into physical contact. That such is not the case is evidence only for the fact that orthopedic surgeons are as fallible as the rest of mankind. Once the control system shuts down, the cell populations come to rest and if continuity has not been restored, none will occur until the system is again perturbed in a fashion bringing the cell populations into activity once more. Obviously, surgical intervention, for the purpose of "freshening" the fracture ends may well be a competent stimulus for restarting the system. The insertion of internal fixation at such a time is merely a more efficient technique for securing immobilization and contact. It should be obvious from this concept that one could restart activity of the cell population by merely simulating the electrical signal of the system without the need to activate the total system. The author would

propose that this serves as the best frame of reference to evaluate the present concepts of electrical osteogenesis. While various electrode materials, methods of insertion and levels of current and voltage are in clinical use, the end result in all is the stimulation of the endosteal marrow cell population. Exactly how this is accomplished at the cellular or cell membrane level must be the subject of careful and intensive evaluation. The necessary techniques are available and should be applied not only in simulated clinical conditions, but also under the operation of whatever natural control system is responsible. An important point mostly overlooked is that we can only crudely approximate the control system signal. Nature produces the appropriate electrical environment without recourse to metallic electrodes. When we utilize such devices, we unavoidably introduce electrochemical events that are not only not normal concomitants of the control system, but may be productive of long term undesirable side effects. Unfortunately, the discipline of electrochemsitry has little information on the behavior of active (current passing) metallic electrodes in the complex biological environment. Since a variety of metallic electrodes have been used in animal as well as clinical studies, a systematic study of the electrochemical events at a similar variety of electrode–biological interfaces is essential to further development in this field. The questions finally narrow themselves down to primarily a consideration of the optimum levels of electrical power introduced. While the authors's clinical program is based upon the levels of current observed to be stimulating to the appropriate amphibian cell population,[9] this may not be the maximally effective range for mammalian cells. Brighton for example, has reported excellent results with stimulating current considerably higher than ours.[14] Therefore a further essential study would be a systematic evaluation of a variety of current/voltage/time conditions as stimuli for the mammalian endosteal–marrow cell population. It should be noted that upon completion of this study and that previously proposed, we would finally be in a position to define the optimum system for electrical osteogenesis utilizing active electrodes implanted into the competent cell population. Bassett has proposed a technique[5] which would appear to obviate most of the problems associated with electrode implantation. If a volume conductor, such as an extremity, is exposed to a varying magnetic field, voltages and currents will be induced within the conductor. Bassett has used a variety of coil systems and magnetic pulses to produce an electrical environment within the tissues which he believes is similar to that resulting from DC current delivered by implanted electrodes. From a purely physical point of view, however, such a system would produce multiple intermittent circular currents within the tissues which would not simulate that delivered by an electrode system operating with direct current. Nonetheless, the possibility would appear to exist that such an environment might be stimulatory to the cells even though it did not exactly simulate the operation of the natural control system. In fact, Pilla has reported specific alterations in cellular function when exposed to the same type of pulsed fields.[29] Unfortunately, there are as many, if not more, basic questions still remaining in regard to this technique. Firstly, few other investigators have used this system in animal studies where careful histological examinations can be done to clearly establish the presence and type of cellular response. Secondly, one cannot view the pulsed magnetic field as a nonbiologically significant factor itself. The overwhelming weight of available evidence now indicates that pulsed fields, both electrical and magnetic, are potent environmental factors for central nervous system functioning.[26] Bassett has demonstrated extremely interesting results with congenital pseudarthosis of the tibia, a disease with a high correlation to CNS disturbances and not a typical nonunion. One could consider this bone regrowth as the result of the pulsed magnetic field acting upon the peripheral nerves so as to correct a functional deficiency of some

type. He has also reported that the pulsed field results in a faster rate of healing in the acute fracture.[4] Since in this condition, the neural electronic system is active, one can also interpret this result as being due to a primary neural effect of the pulsed magnetic field. Urgently needed in this area is a study evaluating the effect of the pulsed magnetic field on established, quescent non-unions. Of similar importance is further investigation of the primary mechanism involved; if it is neural, the possibility exists not only for other clinical uses unrelated to bone, but also for side effects of a different type and magnitude from those potentially associated with the electrode techniques.

For some as yet inexplicable reason, there have been few, if any, attempts to deliberately stimulate periosteal growth with electrical factors. That this growth process does occur is extremely well documented and better understood than the medullary cellular processes concomitant with fracture healing.[35] Since the periosteum may be ascribed a major role in Wolff's law, it would appear to be an ideal candidate for electrical stimulation. On this basis, and since the cellular processes occurring in the periosteum were different from those in the medullary–endosteal complex (mitosis vs. dedifferentiation), the author's group has theorized that it may be responding to the initial electrical potentials noted at the time of fracture. These are of high magnitude, but short duration and we believed them to be derived from the piezoelectric effect associated with the stress to failure. In a preliminary study we applied such potentials to uninjured areas of rabbit long bone periosteum without observing any proliferative response whatever. Conversely, in many of our animal experiments, when electrodes which were originally placed in the marrow cavity became displaced and the periosteum was exposed to DC stimulation, a direct osteogenic response was observed. Obviously, this is another area urgently in need of study; effective stimulation of periosteal growth would be a useful adjuvant to any procedure aimed at restoring continuity to a non-union.

In evaluation of any new clinical technique, a risk-benefit analysis is necessary. Unfortunately, this seems to have been overlooked in the area of electrical osteogenesis. There is not one paper in the entire literature in this field in which long term effects were looked for, While the 20–30 year lead time for malignant transformation in man must await the elapse of that time in regard to clinical objects, it is feasible to approximate this in laboratory animals with shorter life span, and a systematic study of this type is urgently required. While there have been no literature reports of such side effects in the present clinical series, it is the author's contention that this question is decidedly nontrivial, for a number of reasons. The "turning on" of any growth process in which major cellular activity is stimulated carries the inherent risk of malignant transformation either early or late. Theoretically, this would appear to be reduced, the closer the stimulating conditions approximate those occurring naturally. For this reason the author's program utilizes currents in those ranges that can be naturally observed in the course of fracture healing. Currents and voltages productive of measurable electrolysis will result in conditions in the immediate vicinity of the electrode that are necrotizing. While this procedure may be productive of an irritative type bone growth at a distance, the possibility of late untoward changes at the electrode sites must be carefully evaluated. In fact the range of currents and voltages between the lowest levels productive of bone growth stimulation and those clearly locally damaging must be similarly evaluated. As previously mentioned, the physician attempting to simulate the natural healing environment electrically must utilize a nonnatural technique, the insertion of metallic electrodes. Some deposition of metallic cations in the tissues must ensue, even at the lowest

ranges of current and voltage and may similarly be productive of long-term effects. While in the noninvasive techniques involving either capacitative or inductive or inductive coupling, the electrode problems are obviated, one still encounters other problems, some of a novel nature. Field exposure has recently been shown to produce chromosomal abnormalities in malignant cells.[28] Similar changes have simply not been looked for in normal cells and the possibility of their occurrence in cellular systems stimulated into activity would appear to be quite real. In addition, the application of external fields to organisms is accompanied by definite central nervous system effects, the nature of which is not clear at this time. Until answers are obtained bearing on the question of long-term side-effects, particularly malignant transformation, it would appear that the use of these techniques should be strictly limited to those cases of established non-unions proven recalcitrant to all other accepted modes of therapy. The proposal has surfaced from time to time that the techniques of electrical osteogenesis should be clinically utilized as means of accelerating the healing time of normal fractures. This procedure would appear to be particularly hazardous. The cellular activity associated with fracture healing is intense and if it is enhanced, the long term result is generally unpredictable. Furthermore, in view of the fact that the vast majority of such factures heal without complications, such an application would appear to be unconscionable under the risk–benefit concept. It would appear obvious that a program organized around a search for side effects, both long and short-term (without consideration of therapeutic efficiency), is an urgent necessity.

While the technique of electrical osteogenesis is attractive as a solution to perplexing clinical problems, it has raised more questions than it has provided answers, not only in regard to the various techniques now under clinical evaluation, but more importantly in regard to the basic mechanisms responsible for growth and healing in general must be launched. While technically we have advanced but little over the methods Garrett utilized in 1861,[20] conceptually we have opened the door to the application of many new scientific disciplines to the problems of growth and healing. We now have the capacity to place this simple technique upon a firm scientific biological foundation.

The technique of electrical stimulation of growth processes holds the promise for revolutionizing medical practice. The physician for the first time can command nature rather than be its servant and clinical applications presently considered impossible may become commonplace. Electrical osteogenesis may be the opening wedge into the future, its responsible development can bring the future closer sooner; its irresponsible development may well result in again putting off the future for another hundred years.

SUMMARY

The present technique of electrical osteogenesis represents the rediscovery of a method in clinical use over 100 years ago. That technique while reported to have excellent clinical results, was empirically applied and was totally discredited as having no scientific basis. Modern techniques report similarly useful clinical results, but similarly lack an accepted scientific basis. The techniques in present use differ so greatly among themselves that a common mechanism of action seems highly unlikely. Yet all report excellent clinical results. Serious questions are raised concerning the validity of the claims, the mechanism of action and the possibility of long-term undesirable side effects. These questions are not insoluble and the newer physical science disciplines seem well suited to reveal the mechanism of action. Appropriate research projects must be mounted and answers to these questions obtained before the technique is made avail-

able for wide application. The importance of this procedure far transcends orthopedic surgery and bone growth stimulation and if properly pursued, it may lead to revolutionary changes, not only in basic biology, but in the practice of clinical medicine in general.

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