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Direct Current and Bone Growth

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INTRODUCTION

To a significant degree, modern bioelectricity began with the study of the bioelectrical phenomena of bone. An introduction to the subject has recently been published (1), and much of the pertinent literature has been listed (2). My purpose here is to describe only what seem to me to be the most significant developments.

After a brief review of the composition, structure, and physiology of bone, the seminal experiments that led to the birth of bone bioelectricity are described. I paid particular attention to the rationale behind the early studies in the belief that it would be helpful to the reader to see how the threads that were the initiatives of different groups have come together to form the present fabric. It is the work of bold men who broke new ground and who were not deterred by the possibility of making some errors.

After the rush of new ideas in the 1960s, there ensued the present period of consolidation in which the major effort has been the sorting of the wheat and the chaff. A description of this work constitutes the principal part of the balance of the chapter. My view of the basis of electrical osteogenesis best warranted by the present evidence is presented in the last section. 1 think that there is a bright future for the clinical use of direct current for treating bone when the treatment is designed in a manner consistent with that basis.

BONE PROPERTIES

MATERIAL CHARACTERISTICS

Bone is mainly composed of collagen, a protein, and hydroxyapatite, an inorganic calcium salt. Collagen is secreted and then assembled extracellularly to form a matrix on which the hydroxyapatite is deposited, perhaps via epitaxial precipitation (3,4). The processes of collagen polymerization and hydroxy—apatite precipitation occur in a spatial and temporal sequence that ultimately results in the formation of microscopically recognizable layers called lamellae. Lamellation is an end—stage structural pattern; sometimes it is preceded by woven bone, a less organized pattern in which the collagen fibers are randomly arranged like the fibers in a felt. Woven bone occurs in various pathological conditions, but in normal physiology it is an interim material, and is replaced by lamellar bone (5).

Bone occurs in two architectural forms. Compact (cortical) bone, typified by the shaft of the long bones, is relatively dense and its lamellae exhibit several patterns, the most common of which is concentricity around a vascular canal. Cancellous (trabecular) bone is a three—dimensional lacy network usually found inside bones, particularly at the ends of the long bones. Its lamellae, when present, usually run parallel to the trabecu—lae (5). Sometimes, such as in some instances of fracture healing, the cancellous architectural form appears on the out-side of bones as a temporary means of stabilization called external callus.

CELLS OF BONE

Collagen is secreted by the osteoblast, a medium—sized cuboidal cell. Osteocytes are osteoblasts that have become enveloped by bone. They occupy melon—seed shaped lacunae within the bone and form a syncytium via cell processes that extend through channels called canaliculi. Osteocytes might have the ability to remove bone within about 1 micron of the lacunar surface (6), but the major hone—destroying cell is the osteo— clast. Osteoclasts are large multinucleated cells that resemble foreign—body giant cells, but appear to lack the latter’s phago— cytic function (except with regard to the bone). Osteoclasts were previously believed to form via fusion of osteoblasts, but

are now thought to arise from a specialized precursor cell that differs ultrastructurally from the cell that gives rise to the osteoblast (6,7).

Bone—lining cells are extremely flattened cells that cover the surfaces of cancellous and compact bone, as well as the surface of the osteonal canal (8). Although the bone—lining cell is the most common surface cell of bone (6,9), its function is not understood.

Behind the bone—lining cells are the osteoprogenitor cells, the immediate precursors of the differentiated cells of bone (10). Osteoprogenitor cells are capable of division, but the more differentiated cells (with the possible exception of the osteoblast (11)) do not divide.

The undifferentiated mesenchymal cell, which is present throughout the body, is also capable of producing bone in the postfetal organism. It forms heterotopic bone in the presence of an inducer and in certain pathological states, in contrast to the osteoprogenitor cell which forms orthotopic bone in the course of either normal development or repair. The undifferentiated mesenchymal cell and the osteoprogenitor cell are morphologically indistinguishable (12). Whether the former is a less differentiated precursor of the latter is an open question (13), but the distinction between them has been recognized since at least 1952 (14).

BONE GROWTH

The activity of bone is manifested on its various surfaces, each of which, at any given time, is either quiescent, forming, or resorbing bone (15). Excluding disease, there are four bone—forming activities that result in the production of orthotopic bone: development determines size, modeling determines shape, remodeling produces replacement bone, repair restores integrity. Although all bone—forming arises from the activity of osteoblasts, many aspects of the process differ among the listed activities. These include the histological environment in which the osteoblast functions, the pattern of the bone produced, the rate of bone production, the nature of the physiological stimulus that controls the process, and the nature of the artificial stimuli that can affect it. It is helpful to recognize the essential features of the known bone—forming

activities so that they can be compared with the effects produced by electricity.

1. Development

In man, increase in length of bone occurs at the epiphyseal–metaphyseal complex (growth plate), where septa of calcified cartilage are covered with woven bone, thereby creating primary trabecular bone. The woven bone and calcified cartilage core is then removed and replaced by lamellar bone (6). Appositional growth in the developing bones leading to an increase in thickness occurs via periosteal formation of primary trabeculae, compaction to form cortical bone, and then replacement by lamellar bone (6). Periosteal bone growth does not involve the cartilage template step (called endochondral growth) and is termed intramembranous growth. Many factors including diet, drugs, disease, and exercise can affect bone growth in the sense of producing changes in cell kinetics or histomorphology. No factor, however, has been identified that actually controls the growth process. At some level of organization within the developing organism a genetic program is apparently read and executed. Embryonic tibiae when placed in tissue culture will continue to develop for a period in a manner resembling normal growth (16). Consequently, at least a portion of the control system resides in the developing bone itself.

During bone development, endochondral bone formation occurs at the growth plate, and intramembranous hone formation occurs along the periosteum. In both cases, woven hone is initially formed and subsequently replaced by lamellar bone. The intramembranous bone forms at different rates in different parts of a given bone, thereby producing an anatomic phenomenon known as modeling. Enlargement of the cranial vault and development of the ends of the long bones are typical examples (6).

Growing bone exhibits a plasticity principle (sometimes called modeling, sometimes remodeling) which permits it to adapt to mechanical forces by changing its geometry. The healed malaligned fracture is an example. Growth occurs on the concave side and resorption takes place on the opposite side, and the bone ultimately becomes straight. Another example of adaptive growth is the movement of teeth in the jaw caused by orthodontic appliances. In this case, resorption occurs in the portion of

the bone in compression, thereby permitting the tooth to move in the direction of the applied force. The pattern of trabecular bone in the metaphysis is often said to reflect adaptive changes; if it does, that would be a third example of adaptive remodeling. The adaptive response of bone is usually manifest as a modification of ongoing development (as part of the maturation process of the bone), although it also occurs to a lesser extent in adult life (17).

2. Remodeling

By remodeling I mean the process by which existing bone is replaced by lamellar bone. Remodeling first occurs soon after birth when the primary osteons are replaced by the more highly structured secondary osteons that are characteristic of the adult. Remodeling continues throughout adult life as old secondary osteons are replaced by new ones. It is convenient to think of the remodeling of the primary and secondary osteons as a process of replacement of worn, fatigued, or weak bone by a stronger Material, although there is little reason to believe that this is actually the reason that the process occurs. The initial event in remodeling is resorption of bone, followed directly by its replacement by lamellar bone on an equal volume basis (17). Its causes and control system are unknown (17). Remodeling also takes place during repair.

3. Repair

The histological appearance, tempo, and geometry of reparative bone growth depend on many factors including the particular bone and the nature of the injury. Consider for example a traverse fracture in a long bone produced by bending to failure. A blood clot forms in the gap between the bone fragments, and proliferation of the osteoprogenitor cells begins within about 24 hours. In a few days, the clot is replaced by fibrous tissue. Cartilage may appear, particularly if the bone frag— ments are unstable, but it is not an essential constituent of the healing process. When it does appear, endochondral ossification ensues, resulting in the production of woven bone in a trabecular architecture called callus. The callus may occur on toe outside of the bone to form a bridging substance between the fragments, in which case it assures a classic fusiform shape. The callus may also extend throughout the medullary canal in the

region of the lesion. In the final stages of healing, the callus within the medullary canal and the external callus are resorbed, and the callus within the fracture gap along the path of the cortex becomes compacted and remodeled. Ultimately, the fracture gap becomes histologically indistinguishable from the uninjured portions of the bone.

If the bone fragments are rigidly approximated with a compression plate, neither cartilage nor callus are formed, and healing occurs by accelerated remodeling (18).

ELECTRICITY AND BONE: FOUNDATIONS

The beginning of modern bioelectrical research involving bone is generally traced to Iwao Yasuda, a Japanese orthopaedic surgeon (20—22). Yasuda was primarily concerned with the factor responsible for initiating callus formation. He began his work in the 1940's, a time when the realization was developing that bone callus formation was not inextricably linked with bone fracture. A variety of thermal, chemical, and mechanical stimuli were being identified that could produce bone callus in the absence of fracture (19). Yasuda applied mechanical force to long bones and observed callus formation in nontraumatized areas under compression. He also showed that viable and boiled bone yielded an electrical signal when subjected to mechanical deformation. Regions in apparent compression were negative and those in tension were positive with respect to unstressed areas. Yasuda's idea was that callus—producing cells in bone subjected to mechanical and other stimuli were not directly responding to the stimuli, but to a common—pathway signal. He theorized that electricity was the common—pathway signal for callus, and that application of electricity should produce callus. Some tine between l939—1953, he demonstrated that 1-100 μA of direct current (DC) produced callus In the medullary canal of rabbits (20). Thus one form of stimulus that produced callus — mechanical forces —— also produced electricity, and externally applied electricity produced callus.

Yasuda's work was distinctive because it emerged from his analysis of the developing knowledge of bone physiology, and his attempt to synthesize diverse observations. He was not the

first to produce callus using DC current. In 1860, Garratt described the use of percutaneous insulated electrodes in the successful treatment of a nonunion of two years' duration, employing stimulation for 15 minutes a day, every third day, for 9 days (23). But Garratt's and other earlier reports were based on simple empiricism, and stemmed from a time at which electricity was a newly—discovered phenomenon. It was the novelty of electricity rather than its reasoned relevance, that formed the basis of the historical applications of electricity to living organisms.

In 1957, Fukada and Yasuda measured the numerical value of the piezoelectric constant of dry bone (24). Application of a shearing force along the bone axis caused a voltage to appear on bone surfaces parallel to the axis. Conversely, application of an external voltage to bone caused it to mechanically deform. The strength of the piezoelectric effect in bone (the polarization per unit stress or the strain per unit electric field) was about a tenth of that exhibited by quartz.

The first American investigator to report data regarding electricity and bone was the orthopaedic surgeon Robert O. Becker (25—28). Becker began studies of limb regeneration in the late 1950s. His particular interest was the factors that controlled or regulated the process, which he assumed were the same whenever regeneration occurred throughout the vertebrate phylum. The existence of surface electrical potentials (SEP) (slowly varying millivolt—strength electrical potentials that can be measured between any two points on a surface of a living organism) had been known for many years, although their origin and physiological significance remained unascertained. It had been suggested that SEPs were significant factors in embryonic development, and that they served to guide and perhaps determine organization, differentiation, and specialization in the developing organism (29,30). Since the time of Galvani, the existence of electrical changes at an injury site had also been known. Becker combined the two observations and hypothesized that the SEPs might have a role in the control of the regenerative process. He measured SEPs in salamanders, and observed a spatial pattern that roughly corresponded to the nervous system of the animal (25). He believed that the SEPs originated in neural or perineural tissue, and he concluded that the

complexity of the pattern made it a candidate as a control mechanism for regeneration (26,27). Becker regarded the association with nerves as particularly important, because Singer had previously shown that the presence of a critical amount of nerve tissue within the amputation stump was required for regeneration to occur (116).

Becker amputated the forelimbs of salamanders (a regenerating species) and frogs (non—regenerators) and measured the SEP at the distal amputation stump relative to the proximal uninjured tissue in the limb (26). He found that the characteristic response following amputation was the occurrence of a positive spike in the SEP within about 1 day of the amputation, followed by a decrease to 20—30 mV at 5—10 days following amputation. Thereafter, the potential at the amputation stump approached the normal (negative) value from the negative side. The frogs also exhibited a positive peak within about a day of amputation, but thereafter the SEP decreased monotonically toward the normal (negative) value from the positive side. Thus, Becker identified a negative SEP, measured relative to adjacent uninjured tissue at about 5—10 days after amputation, with the phenomenon of regeneration.

Fracture—healing is also a regenerative phenomenon, and Becker found a similar temporal change in the SEP following a fracture of a long bone in the salamander (26). Again, the normal negative SEP at the fracture site became positive following fracture, and then became negative at 10—15 days thereafter.

Zachary B. Friedenberg, an orthopaedic surgeon at the University of Pennsylvania, conducted a detailed study of the SEP in fractured limbs of rabbits and patients (117). When Friedenberg’s data is expressed similarly to that of Becker’s (SEP at the injury site relative to adjacent uninjured tissue), it also shows that the Injury site became positive (relative to uninsured bone) immediately after fracture, as described by Becker. In 16 patients with healing tibial fractures, the hone remained positive (relative to the proximal epiphvsis), in apparent distinction to the negative values that were recorded by Becker in animals.

Becker presented his SEP data on regeneration and fracture healing at the 1961 meeting of the American Academy of Ortho—paedic Surgery, and it led to a short but important period of

collaborative research with C.A.L. Bassett, an orthopaedic surgeon at Columbia University. Bassett was particularly interested in the physiology of bone formation, and their mutual interest centered on the question of the control process for adaptive remodeling. They reasoned that electrical potentials had been associated with regeneration (citing Becker's work, and other references previously cited by Becker), and that electrical potentials might also be the basic link in the clinically observed adaptive response that occurs in children with healed malaligned fractures. In 1962, Bassett and Becker reported that moist human and frog bone yielded an electrical signal when subjected to cantilever bending (31). The signal decreased by only 5% when the tissue was dried, and was asymmetric in the sense that equal and opposite voltage pulses were not seen attendant loading and unloading the bone. Regions of the bone in apparent compression (concave side) were negative relative to regions in tension.

The interpretation of the stress—generated signal in terms of adaptive growth was subsequently described more fully (32). The endogenous electrical phenomenon was hypothesized to be capable of directing the activity of bone cells in such a way as to account for bone's adaptive behavior. Formation of insoluble bands of collagen was reported to occur when DC currents were passed through solutions containing collagen molecules. Based on this observation, the stress—generated signals in bone were hypothesized to also be responsible for orientation and extra—cellular aggregation of collagen (32).

I observed formation of bands in previously clear solutions of rat—tail tendon collagen within a few minutes of the initiation of current (1—75 μA) (33). The bands formed only in regions where the pH was raised above about 3.5 as a consequence of electrochemical chances at the cathode. Raising the pH of the collagen solution to 5.5 by the addition of sodium hydroxide quickly precipitated the collagen. Thus, if stress—generated electrical signals in bone do not alter local pH —— there is no good evidence to indicate that the; do —— then it is unlikely that they can have the hypothesized non—cellular consequences.

What was the origin of the stress—generated electrical signals? It was argued that piezoelectricity could not account

for the signals measured in bones that contained their normal water content (wet bone) because a piezoelectric material yields a symmetric signal upon application and release of the applied force, whereas asymmetric signals had been observed (32). In addition, both Becker and Bassett were conceptually dissatisfied with the piezoelectric mechanism as the source of the bone potentials because they believed that its inherent symmetry was inconsistent with its putative role in regulating adaptive bone growth. The idea was that a symmetric signal could not direct a long—term growth process because it was inherently incapable of sending a net signal to a target cell.

To explain the observed signal asymmetry, it was suggested that the molecular structure of the interface between collagen and hydroxyapatite actually formed a PN junction diode (32). Shamos and Lavine analyzed the measurement technique employed, and concluded that the electrical signal manifested by the wet bone was intrinsically symmetrical, and that the apparent asymmetry resulted from the choice of measuring circuit (34). Another factor that probably contributed to the observed asymmetry in voltage was viscoelastic flow (35).

Cochran made extensive measurements of stress—generated electrical signals from wet bone, which he assumed were due to the piezoelectric effect (36). He measured the signals produced in precisely machined strips of bone maintained under physiologic conditions and subjected to cantilever bending. The signal was a relatively insensitive property of the bone, and exhibited only minimal variation with thickness or physical treatment (boiling, autoclaving, formalin fixation, radiation with 100,000 r, heating to 200^{0}C). On the other hand, the signal was obliterated when the porosity of the samples was changed by demineralization.

During 1962—1968 most investigators assumed that the stress—generated electrical signals from bone were piezoelectric in origin, irrespective of whether they were observed in wet or dry bone. This perception was altered by a dawning recognition of the existence of a class of electromechanical phenomenon in wet tissue called streaming potentials (37).

The nature of streaming potentials has been described by Pollack (35). At the interface of a solid and an ion—containing fluid, specific interactions occur resulting in surface—bound

charges and in the creation of a region in which the ionic charge distribution differs significantly from that of the bulk fluid. The electrically altered region in the fluid phase is called the diffuse layer, and its boundary with the bulk fluid is the slip plane. The electrical potential at the slip plane is the zeta potential, and when it is zero the solid is said to be at its isoelectric point. If the diffuse layer is caused to move tangentially to the surface, the electrical potential of the slip plane is altered; this kinetic modification of the electrical potential at the slip plane is called the streaming potential. It is created by motion of the diffuse layer whenever the fluid pH is such that the surface is not at its iso—electric point.

Anderson and Eriksson reported the occurrence of a signal of the order of millivolts in tendon subjected to repetitive impulse loading; the signal vanished when the pH of the bathing fluid was such that the tendon was at its isoelectric point (39). From the absence of the voltage at the isoelectric point, they concluded that all electromechanical phenomena in wet tendon arose from streaming potentials and that piezoelectricity was absent from wet tendon. They performed similar experiments with bovine bone (40), and concluded from the observed change in the piezoelectric constant with pH, that streaming potentials were present in wet bone but could not completely account for its electrical signal.

It was not logical to conclude from the absence of an electrokinetic signal at the isoelectric point of human tendon that wet tendon was not piezoelectric. Another interpretation -- and as it turned out, more probably the correct one —— was that the piezoelectric signal was simply not detected by the measuring system employed. Subsequent studies showed that wet biological tissue, including bone, are piezoelectric (41—43).

Streaming potentials are undoubtedly the physical basis of the electrical signals observed in wet bone (36), tendon (39), and cartilage (44,45) subjected to mechanical forces and measured with wick electrodes or metallic electrodes coated on the surface (46,47). The millivolt—strength signals disappear as the tissue is dried, and are replaced by microvolt—strength signals of piezoelectric origin (48) which were previously undetected because of rapid neutralization by the ions in the

diffuse layer.

Whether the piezoelectric signal, which is not conveniently measured in wet bone, or streaming potentials (or possibly other mechanisms) should be identified with the electrical signal that hypothetically helps to mediate some bone adaptive responses has not been resolved. One reason that disposes me to the choice of piezoelectricity is the data obtained by McElhaney, who measured the piezoelectric charge distribution that appeared on the surface of an intact, embalmed, human femur (49). The bone was dried at 105°C for 2 weeks to remove adsorbed water, and more than 600 square electrodes (0.25 inches on a side) were attached. The ends of the bone were embedded in epoxy, and it was vertically mounted and cyclically loaded in compression (50—100 pounds, 1 Hz). Measurement of the charge appearing on each electrode yielded an apparent random distribution of positive and negative areas that did not correlate with stress distribution, wall thickness, curvature, or other topological features of the bone. Measurements made on sections cut from the bone and loaded in pure compression revealed a surface—charge distribution whose sign and magnitude varied strongly with circumferential position.

McElhaney’s data included a posterior view of the outline of the right femur used in the study, showing the actual measured surface—charge densities. If the piezoelectric surface charge could act as a mediating factor in an adaptive osteogenic response, I reasoned that McElhaney’s data ought to be interpretable as an adaptive signal according to a self—consistent scheme. I interpreted the medial and lateral charge distributions as signals to build or resorb bone in an amount directly proportional to the measured charge density (50). On the medial surface I identified a negative surface charge with bone building, and a positive surface charge with bone resorption. On the lateral surface the positive and negative surface—charge densities were identified with bone resorption and deposition respec—tively. An adaptive response (self—consIstent change in femoral outline) was produced, and the integrity of the femur was reserved, as opposed to a random pattern that was expected if the measured charge distributions were unrelated to bone adapta—bilitv (50).

McElhaney demineralized some of the sections of the bone in

an attempt to ascertain the origin of the piezoelectric effect, but found that the bone matrix samples were too flexible, and hence unsuitable for piezoelectric measurements involving the application of stress. I employed a method developed by Fukada (24) in which an electric field is applied to the sample and a strain is measured (converse piezoelectric effect). Using this technique, I measured the piezoelectric effect in air—dried bone, and then chemically removed the bone mineral from half the samples and the bone collagen from the other half. The piezo—electric effect was manifested in the demineralized samples, but was absent in the decollagenated samples (51).

In addition to pursuing the role of stress—generated electrical signals in adaptive growth, Becker continued his study of the physiological significance of the other endogenous electrical property of bone —— the SEP. From a time—sequence study of fracture healing in the tibiofibularis of frogs, Becker and Murray concluded that the cells of the fracture callus originated from the erythrocyte, and not from mitotic activity of osteoprogenitor cells as occurs in the healing of mammalian fractures (52). They described a sequence involving the dedif—ferentiation of the nature amphibian erythrocyte into a stem cell, and its subsequent redifferentiation into the connective tissue cells capable of repairing the injury. They hypothesized that the SEPs at the injury site mediated the reparative response. The electrical events measured within several hours of the fracture were held to originate with the bone substance itself, and to have occurred as a result of the persistence of a residual stress in analogy with a phenomenon reported by Bonfield and Li (53). Electrical phenomena previously identified and associated with neural tissue (26—23) were felt to provide the subsequent control function of the healing response (52). To substantiate the portion of the theory dealing with the stimulus for dedifferentiation of the nucleated erythrocyte, Becker and Murray subjected amphibian erythrocytes to DC currents of 1—1000 μA, and directly observed a remarkable sequence of morphological changes in individual cells that was similar to the known maturation sequence the amphibian eryth— rocyte, but which proceeded in the reverse direction —— from erythrocyte to stem cell.

The occurrence of a dedifferentiation response of amphibian

red blood cells was subsequently verified (54), but the factors responsible for its initiation when it occurs *in vitro* remain unclear. Dedifferentiation occurred in cultures through which DC current was not passed, and was attributed to the presence of static charges on the plastic chambers (52). The sequence of cellular changes was also observed at widely different current levels, leading the investigators to conclude that the sex and hormonal status of the donor were important factors in the response threshold.

APPLICATION OF ELECTRICAL ENERGY

INITIAL STUDIES

Bassett and Becker reasoned that if stress—generated electricity could directly affect bone cells thereby mediating adaptive bone growth, then externally applied electricity ought to affect bone growth in a polarity—dependent fashion. In particular, the negative electrode should be associated with growth, and the positive electrode with resorption. This view, which cane from their considerations of the natural history of the healed angulated fracture (55), was tested in a controlled study in dogs reported in 1964* (56). Holes were drilled through one cortex of the femur, and platinum electrodes were inserted into the medullary canal. A simple series circuit was used to supply DC current to the electrodes, and inactive platinum electrodes were implanted in the contralateral femur. After 21 days, woven bone trabeculae were found at the active and control electrodes, but the greatest amount of grossly observable new bone occurred at the cathode. The current associated with the effect was about 3 μA.

The authors interpreted the data as supporting the hypothesized linkage of electrical negativity with bone growth and positivity with bone resorption, with the proviso that the failure to observe resorption at the anode was probably due to the

* It is incorrect to view the concave side of a healed malunited fracture as being in compression (57,58). It is incorrect to view bone in compression as being electrically negative, whether it is wet (59) or dry (49,60). Despite this, both ideas remain popular.

non-physiological nature of the electrical signal (continuous application for 21 days, rather than an intermittent electrical signal that would be associated with an adaptive osteogenic response). Another interpretation was that the observed osteogenic response was unrelated to the conceptualization that actually led to the study, but was basically an inflammatory response.

The experiment was repeated by O'Connor et al. with the incorporation of a numeric scale to quantitate the amount of bone formed at the electrodes (evaluation of X-rays by five naive observers) (61). In 7 of the 12 dogs studied the cathode had the most bone associated with it, but in 2 dogs it had the least. None of the average scores of the 4 electrodes (cathode, anode, proximal control, distal control) differed from the others by the paired t test.

Hambury et al. drilled holes through the cortex of both sides of the femur of rabbits and inserted platinum electrodes that were cut to end flush with the periosteun (62). An effective current of 3 μA was passed continuously for 21 days, and the extent of bone growth was then assessed quantitatively by measuring the strontium-85 uptake on the 21st day after surgery. In 17 animals, 7 had more bone growth near the active implant, 9 had more bone near the inactive implant, and in 1 animal there was no difference. Thus, the passage of 3 μA for 21 days could not be distinguished from the osteogenic response that occurred in response to the drilling of the holes through the cortex of the bone (as determined by strontium-85 uptake). Failure to observe electrical osteogenesis was also reported by Crelin and Dueker following implantation of electrical circuitry in mice for 2 weeks (63).

A major difficulty with DC studies of electrical osteogenesis in the late 1960s was the inability to control dose. The typical implanted circuit consisted of a battery in series with a resistor: such a circuit does not function at a predictable current level in the complex environment of animal tissue. This difficulty was overcome by Friedenberg et al. who employed current-controlled implantable circuitry, and thereby categorically established electrical osteogenesis as a real phenomenon (64). Two holes (1 cm apart) were drilled into the medullary canal in the rabbit femur. Stainless-steel electrodes were

placed in the bone holes, and constant currents of 1, 5, 10, 20, 50, and 100 μA were administered in separate groups of animals. All the rabbits were sacrificed after 10 days, and both bone production and tissue destruction were analyzed at each electrode using semi—quantitative histology. It was concluded that 5—20 μA was optimum for bone formation at the cathode, and that tissue destruction occurred at the anode at currents as low as 1 μA (64).

ACCELERATED FRACTURE HEALING

The observation (56) and unequivocal verification (64) that electricity could make bone grow was largely a result of speculation about the nature of the control system for adaptive remodeling. About 1970, the thrust of the research in bone bioelectricity shifted rapidly to the essentially pragmatic consideration of whether and how electrical osteogenesis could best be used in the clinic.

In 1971, Friedenberg et al. reported data concerning the effects of DC current on fracture—healing in rabbits (65). Following bilateral fibular fractures, rabbits were divided into S groups depending on the position of the electrodes relative to the fracture site. All animals were recovered l8 days after fracture. There was significantly more callus (determined by X—ray evaluation) in the animals that were stimulated with the cathode in the fracture site (all animals received 10 μA). Mechanical testing revealed stiffer fibulae on the treated side.

Many subsequent studies in animals shoved that DC currents could cause more callus formation at an injury site than would have otherwise occurred, and this condition was commonly called accelerated healing (66—69). In one such study (66), following bilateral osteotomies of the radius in rabbits, an electrode (it is unclear whether it was gold or platinum) was placed in the bone near (but not at) the osteotomy site. The other electrode was placed on the skin. Accelerated healing as determined by the roentgenologic appearance of periosteal callus was found only when the implanted electrode was a cathode; the maximum effect occurred at 15-20 μA. In the treated osteotomies, the periosteal reaction was seen at 1.5-2.5 weeks after surgery, which was about a week earlier than the bony callus that formed on the control side.

Connolly et al. (67) placed stainless steel pins above and below transverse osteotomies in dogs and passed 10—30 pA for 3—12 weeks. In a series of 70 dogs, a tendency for greater callus formation in the stimulated bone was noted based on mechanical testing, measurement of callus weight, and bone ash weight.

Rabbits were subjected to bilateral diaphyseal tibial osteotomies, and the bone fragments were fixed with compression plates (68). Holes for electrodes (material not specified) were drilled 5 mm above and below the osteotomy site, and 3—15 μA were passed for 21 days. Inactive electrodes were implanted in the contralateral tibia. The breaking strength of the tibias was 21% greater on the stimulated side ($P < 0.01$, paired t test). The DC current apparently elicited periosteal and endosteal callus which added to the mechanical strength of the osteotomy site (68). Accelerated healing of mandibular slot osteotomies (7x2 mm) was reported in dogs using 12 μA at 0.7 Hz (69). At 21—35 days more bone was present in the defect on the stimulated side as determined by gross examination, X—ray, and histological examination.

NON-UNION ANIMAL MODELS

Several attempts have been made to study the effect of electrical stimulation in a nonunion animal model. In one study, 58% of 57 radial osteotomies in dogs failed to heal in 12 weeks in the absence of internal fixation (70). The addition of 20 pA via platinum electrodes to the osteotomy site did not significantly alter the incidence of nonunions (55% of 13 oste—otomies). The duration of the 12—week post—implant period during which the current actually flowed is unclear (70). Other animal nonunion studies reported more success (71—72).

A 1.5—cm section of the midshaft of the tibia in dogs was removed and replaced with a block of silicone (71). Eight weeks later, the silicone block was removed and the defect was extern-ally stabilized. lout aces later, a stainless-steel cathode was placed in the defect and platinum anodes were inserted into the medullarv canal through bone holes located 1.5 cm above and below the defect. A current of 20 μA was passed for 4 weeks in 22 dogs, and an equal number of dogs served as sham—implanted controls. The existence of clinical union, the extent of

technitium—99 activity, and the histological appearance of the defect were evaluated semi—quantitatively. Based on all three criteria combined, the data indicated superior healing on the treated side (Wilcoxon test, $P < 0.01$)(71). When the criteria were evaluated individually, clinical union, but not histological appearance, was statistically improved on the treated side ($P < 0.05$) (71).

In a similar study (72), the investigators stabilized the bone using an intramedullary rod through the silicone block. Eight weeks later, the rod and block were removed and a titanium cathode was placed in the defect. Rigid external fixation was achieved via transtibial pins connected by stainless—steel rods. The procedure was performed unilaterally on 30 dogs, which were recovered at 4, 8, and 12 weeks after implantation of the titanium. Half the animals in each group were stimulated using 20 μA (a platinum wire in the thigh was the anode), and the remaining animals served as controls. The response in the controls indicated progress toward a nonunion. An osteogenic response was observed at 4 weeks, both radiographically and histologically, but the extent of the response appeared to decrease at B and 12 weeks (72). An opposite trend was seen in the stimulated animals. Significantly less bone was present in the stimulated limbs compared to the controls at 4 weeks, but significantly more bone was present at 12 weeks after initiation of current flow. In contrast to the report of Friedenberg et al. (73) the bone that formed at the cathode did not occur in direct apposition to the wire.

The DC resistance (about 50,000 Ω) and the AC impedance (200—500 Ω) each remained essentially constant throughout the 12—week period (72). This data tends to devaluate any hypothesized importance of the role of time dependence of the electrical properties of bone in determining its biological response to an impressed voltage.

It is difficult to understand why the osteogenic response that occurred in the stimulated limbs following the second surgical procedure was reduced at 4 weeks, but increased at 12 weeks postoperatively compared to the control (72). It’s as if the DC current sent two signals: one to build bone, and one to retard the process of bone building that had been triggered by another factor (removal of silicone block and intramedullarv

rod). Over time, their relative importance reversed, and the balance tended to favor the bone—building process.

THE MEDULLARY-CANAL MODEL

Friedenberg et al. (73) developed an animal model in which the role of the healing response to a defect in cortical bone was eliminated. A stainless—steel electrode entered the tibia of a rabbit at the level of the tubercle, and was passed down the shaft such that its uninsulated portion (1 cm) was located about 5 cm distal to the drill hole. The medullary electrode was operated as a cathode, and the electrical circuit was completed using an anode in the soft tissues of the thigh. DC current was applied for 21 days, and monitored regularly throughout the treatment period. The amount of intramedullary bone growth that occurred in a 2—cm section of the bone centered over the 1—cm exposed portion of the electrode was measured.

A technique was developed to quantitate the extent of bone formation in the medullary canal. A grid was superimposed on a cross—sectional image of the bone at the level to be measured, and the number of intersections on the grid that overlaid bone was determined and converted into an index that expressed the percentage of the medullary cross—sectional area occupied by bone. Merely placing the electrode in the medullary canal caused an increase of 1—2% of new bone growth in the canal. At 5—10 μA, the portion of the cross—sectional area of the canal occupied by new bone was increased to about 5%, indicating that bone callus formed around the cathode. Animals that received 20 μA exhibited about 20% new bone growth in the canal (more than 10 times the amount of bone produced by the inactive control electrode). Again, no histological changes occurred in the cortical bone adjacent to the callus. The highest current that could be accommodated by the walling—off response alone was 20 μA. At 30 μA, only 14% new bone was formed, and there was histomorphological evidence of tissue damage including destruction of marrow elements, enlarged Haversian canals In the cortical bone, and empty lacunae. These observations were made in 2 of the 6 animals that received 30 μA, in 4 of the 6 animals that received 40 μA, and in all animals that received 52 or 100 μA. Even at 100 μA, the extent of the reaction did not include the periosteum, which was unaffected in all animals.

Increased vascularity in the marrow cavity was also reported.

Increased vascularity, and the absence of mechanical instability at an injury site are factors that, separately, favor intramembranous bone formation (14), and this is what was observed (73) (cartilage was encountered only occasionally).

Histological examination of the DC—induced intramedullary bone revealed that it resembled a well—developed fracture callus (73). The implication, therefore, was that electrically induced bone was actually reparative bone and that the cells responsible for its formation were the same as those responsible for bone formation following a non—electrical stimulus. This idea was supported in a study in which the intramedullary model was modified to allow for recovery at 2—28 days after electrode insertion (bilateral implants, with 20 μA delivered to the right tibia) (74). Cells having essentially identical ultrastructural characteristics appeared on both sides (74). Even when initiation of electrical stimulation was delayed for 28 days following surgical insertion of the electrode (to allow for the trauma of insertion and the osteogenic effect of the presence of the wire in the medullary canal to become a minimum), distinctive ultra—structural characteristics on the stimulated side were not observed.

ROLE OF SIGNAL ELECTRICAL CHARACTERISTICS

Perhaps the most interesting aspect of the DC—induced callus formation reported by Friedenberg et al. (65,73) was its apparent localization to the cathode —— the observation fit well with the original rationale (56) for applying DC current to bone. But in 1972, Richez et al. (75) used platinum electrodes, and did not observe a polarity—dependent effect. Three holes (2 cm apart) were drilled into the medullarv canal of the humerus of rabbits, and a platinum electrode (an anode, cathode, and control electrode) was placed in each hole. A current of 50 μA was passed for 1 second, and during the next second the stimulating electrodes were short-circuited. Stimulation was administered continuously for up to 3 weeks. A second treatment group received 250 μA for 1 second followed by a short-circuiting that lasted 9 seconds. A similar osteogenic response was seen at both active electrodes in the medullary canal, consisting of the formation of a trabecular network surrounding

the electrode. The inactive electrode was simply covered with fibrous tissue. No differences in response were seen using the two stimulation signals (75).

Other reports also indicate that electrical polarity is not a fundamental factor in electrical osteogenesis (76—79). Two parallel osteotomies, 0.4 inches apart, were made normal to the sagittal suture and posterior to the coronal suture in the calvaria of rabbits (76). The defects were stimulated 15 hours/day, 6 days/week, for 3 weeks using platinum electrodes (anterior anode). The amount of bone present in the defects at sacrifice was determined by measuring the optical density of high—resolution radiographs of the excised calvaria. For reasons that were not explained, the control anode exhibited less healing than the more posteriorly located control cathode (4% vs. 35%). When the defects were stimulated using 10 μA DC, the amount of bone present at the electrodes was increased by roughly the same proportion at the anode and the cathode (4% increased to 8%, compared to 35% increased to 65%) (76).

A current of 7.5—30 μA administered via platinum electrodes inside the proximal metaphysis of rabbits produced alterations in the trabecular pattern (77,78). A reparative response occurred consisting of woven bone, and the histomorphological pattern was the same for both anodes and cathodes at the proximal meta—physis (in each case the other electrode was placed near the distal metaphysis).

In 20 dogs stimulated for 4 weeks via intramedullary electrodes, significantly more bone growth was seen at the anode as compared to the cathode (electrode material not specified) (79).

Current density can be an important factor in determining the magnitude of an osteogenic response. In a study by Chamoun et al. (SO), two kinds of 1.4—mm—diameter stainless—steel cathodes were used; one was threaded (3 threads per mm), and the other was insulated except for S holes, 7.36 mm in diameter, that were drilled traversely through the electrode. The current density of the threaded electrode was smaller by more than a factor of 100, and It produced 20 times as much bone in the medullary canal (evaluated after 21 days’ treatment) when both electrodes were powered with 20 μA (8O).

Brighton et al., in 1981, presented evidence to indicate that pulsed DC currents were less effective than DC current in

producing an osteogenic response in the rabbit medullary cavity (81). Stainless—steel electrodes were implanted. bilaterally in rabbits, and one side was stimulated with DC while the other side was stimulated with l—msec current pulses having an amplitude equal to that of the DC current (20 μA). The pulse repetition rate was varied from 10—750 Hz, but the pulsed current offered no advantage over direct current (Table 1).

IN VITRO STUDIES

Norton and Moore exposed pieces of 5—day—old rat calvaria in tissue culture to intense, low—frequency electric fields (100 kV/m, 5 Hz), in an experiment to determine whether bone development could be altered via the converse piezoelectric effect (82). Aberrant growth consisting of the formation of woven bone trabeculae was described. It is not possible to rule out a direct effect on the bone cells, or other phenomena such as an ozone—mediated effect (ozone is frequently associated with high—intensity electric fields). Nevertheless, the report provides some evidence that external electric fields can alter bone development in vitro.

An important experiment by Treharne et al. demonstrated that electrical energy could produce an osteogenic response in vitro (83). Fetal rat tibiae were grown in vitro for 8 days during which time they were subjected to 5—20 μA DC. The current was administered by passing a pointed stainless—steel cathode through the bone surface into the medullary canal. The circuit was completed by operating the stainless—steel raft on which the hone was placed as an anode. The thickness of the bone wall in the vicinity of the penetrating cathode was measured, and the tibiae that received 10 μA were more than 50% thicker than the controls. At 20 μA, the DC—induced increase in bone thickness was about 80%.

It follows from the Treharne et al. study that applied mechanical forces, the presence of neural tissue, and substances in autologous blood are all not required for electrical osteo—genesis. In at least one instance electrical osteogenesis was observed in culture media that lacked the fetal calf serum that was usually present (110); this suggests that no blood—born substances are required for the effect. It would have been interesting to determine whether electrically—treated culture

medium would have produced similar responses in bone growth, thereby directly implicating the electrochemical products produced at the electrodes.

Aro et al. (84) cultured callus fragments from 9—day rat tibial fractures, and cells that grew out of the explant were innoculated into 3.5—ml of culture media and electrically stimulated (100 μA pulses, 8 msec duration, 0.8 Hz repetition rate) using platinum/iridium electrodes. Cell confluence was reached about 80 hours after innoculation. The stimulated cell cultures showed a transient increase in tritiated thymidine uptake (but not in numbers of cells) at 33 hours after innoculation. The authors interpreted the study to indicate that cells from fracture callus were sensitive to electrical signals in vitro, but an equally valid interpretation is that the cells responded to the electrochemical byproducts produced at the electrodes.

CLINICAL STUDIES

The first systematic controlled study of the clinical efficacy of electrical osteogenesis was a report by Jorgensen involving accelerated fracture healing. He devised a clinical procedure for characterizing the degree of healing of tibial fractures (85—87), and applied it to the determination of the effect of electricity (88).

The procedure was built around an external fixation device commonly used to stabilize fractures of the long bones (Hoff—mann). The stabilization device itself consisted of 2—3 pins drilled into the anteromedial face of the bone, 6 cm proximal and distal to the fracture site, and a metal bar that was attached to the pins to prevent movement at the fracture site. The bar could be replaced by a unit consisting of two separate metal bars and a micrometer, designed such that the micrometer would directly register the relative displacement of the bar ends along their axis when the tibia was loaded in bending. For the small deflections involved in evaluating the mechanical strength of the healing fracture, the angular deflection of the tibia when subjected to bending could be evaluated as the quotient of the micrometer reading and the distance of the measuring axis to the center of the bone (85). The leg was held by the examiner proximal to the proximal fixation screws, and loaded 6 cm distal to the distal fixation screws with a force of

5 kg (the bending plane was perpendicular to the anteromedial surface of the tibia). Working with autopsy specimens, Jorgensen found that the average deflection of the intact bone in women (average age 60) was 0.40, and the average deflection in men (average age 65) was 0.20 (85).

In a group of patients having tibial fractures fixed with the Hoffmann apparatus, Jorgensen measured the tibial deflection at a time in the healing process at which the patients were clinically judged to be capable of full weight—bearing. Readings were made in the anteromedial and the posterolateral direction (which tended to open and close the micrometer gap, respectively) and then averaged. In 40 patients with fractures in the middle or distal third of the tibia, he found that 32 patients exhibited a deflection of 10 or less at the time they were judged to be clinically healed (86,87). Thus, a deflection of l° was associated with full weight—bearing in a healing tibial fracture.

In another study, patients with fresh tibial fractures (2—10 days) were given electrical stimulation via the trans—tibial metallic pins (88). The applied current consisted of a constant component of 20 μA, and a 1—Hz component (intended to simulate signals that may be produced during walking) that had a peak value of about 500 μA. Following stabilization of the fracture, the patients were randomized into treatment and non—treatment groups, and the time required for healing to proceed to the point where the fracture was stable (exhibited less than 1° of bending) was determined. The polarity of the pins was reversed periodically throughout the course of the treatment.

The data showed that the clinical endpoint was reached more quickly in the stimulated group. In the series of 57 patients, 87% of the stimulated patients were healed (by the 1° endpoint) within 3 months, whereas only 45% of the control patients exhibited the endpoint ($P < 0.001$).

The patients apparently received continuous stimulation, but neither the extent of patient compliance nor the dependabil—ity of the stimulating device was discussed. It seems likely that there were significant times during the healing periods during which there was no stimulation.

Another study in which DC current was employed in an attempt to hasten the normal healing process in patients was

reported by Mazureik and Eriksson (89). Forty patients with jaw fractures (anterior mental foramen) were treated with 10—20 μA via a platinum cathode percutaneously placed near the fracture site. The extent of the mobility of the fracture site was assessed clinically after 14 days. Of the 40 patients treated, 36 had a mobility ranging between excellent and good, whereas of 40 control patients, 35 had an estimated mobility between poor and fair. There was no difference in mobility between the groups after 6 weeks (the full period of immobilization of the jaw fracture in the study). The mobility of the jaw fracture in 5 stimulated patients and 5 control patients was quantified employing a device that measured the displacement of the bone fragments that occurred when a standard (1 kg) force was applied. The data parallelled the clinical observations (Figure 1).

The most frequent clinical use of electrical osteogenesis involving DC electrodes has involved the treatment of nonunions, which are fractures (usually of the long bones) that have failed to heal as expected. Several investigators have reported data from small groups (90—92), but the most complete studies have been performed by Carl T. Brighton, an orthopaedic surgeon at the University of Pennsylvania, and his colleagues (93—96).

In the Brighton procedure, electrodes were drilled into the nonunion site such that the bare tip (1 cm) of each stainless—steel cathode came to lie directly in the nonunion site (usually in the femur or tibia). The wires emerging from the leg were bent parallel to the leg and connectors were clamped to the exposed ends; the anode was a conducting pad placed on the skin. The power source was attached to the electrodes via the connectors and enclosed in a bandage, and a plaster non—weight—bearing cast was applied. Electricity flowed continuously for 12 weeks, and was monitored once every 4 weeks. Following 12 weeks' treatment, the cast and electrodes were removed and X—rays were made. Typically, the X—rays showed only little healing at this stage of treatment, and continued immobilization for another 12 weeks, without electricity, was provided. The initial report involved 57 patients who had an average duration of nonunion of more than 3 years (93). Among the first 18 cases, were 4 cases involving nonunion of the medial

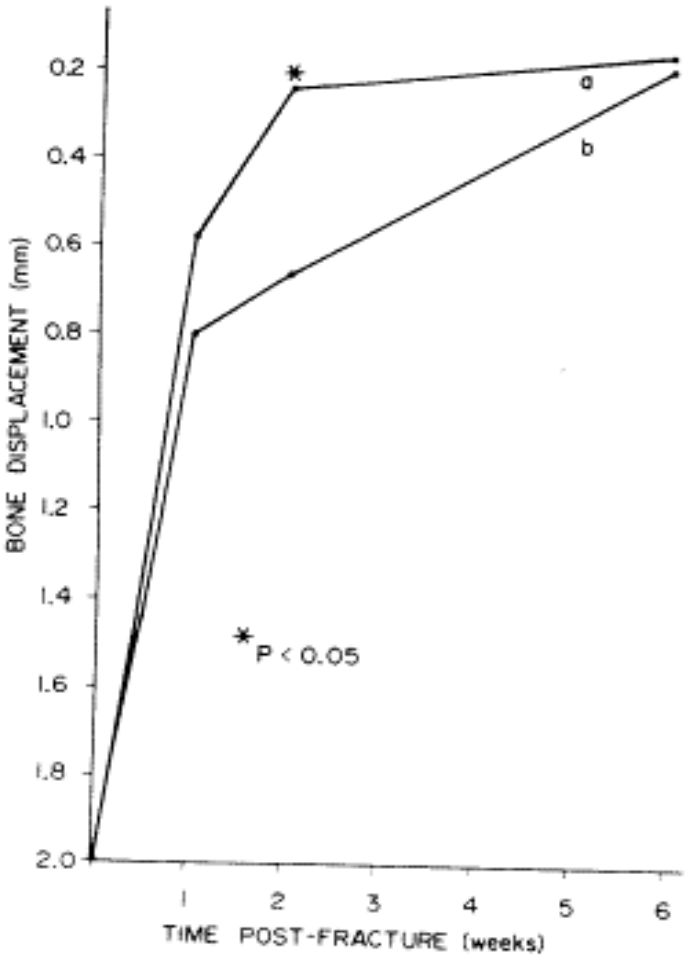

FIGURE 1. Average displacement of bone fragments for an applied force of 1 kg in patients with mandibular fractures (N = 5 in each group) (89). (a), (b) treated and control patients, respectively.

malleolus; each was treated using 10 μA, and each healed. One of 2 nonunions in the clavicle healed, but only 2 of 12 non—unions in a long bone healed. The data was interpreted to indicate that 10 μA administered via one percutaneous electrode was sufficient for a small bone like the medial malleolus, but was insufficient for a larger bone like the tibia. The use of 4 electrodes for the tibia or femur then became the standard procedure, with each electrode delivering 20 μA. Of the next 39 patients treated, 28 healed during the first attempt (72%).

The investigators concluded that the healing was due to electricity alone, and was not due to the cast immobilization. They reasoned that since the average duration of nonunion prior to treatment was 3.3 years, it would be unlikely for 12 weeks' immobilization alone to have brought about the therapeutic result.

The argument is obviously not conclusive, but it is plausible. To merely cast immobilize a 3—year—old nonunion is not a recognized therapeutic treatment. It therefore seems unjustified to impute a therapeutic consequence to this step when it is employed as part of a treatment regimen.

A factor that could falsify the assessment that the healing was due to electricity alone is the effect on the bone associated with drilling in the electrodes (which were actually Kirschner wires). In some cases the electrodes were passed into the nonunion gap through soft tissue, but in other cases they were drilled in through cortical bone. The investigators did not distinguish which technique was used in the various cases. A healing response will be initiated by the trauma associated with drilling through bone. Indeed, that was one of the reasons for developing the medullary—canal model (73). The possible role of mechanical stimuli delivered to the treatment site also does not seem to have been adequately considered. Although immobilization alone is not likely to have been a therapeutic factor, the chronic mechanical stimulation delivered to the treatment site by small mechanical motion of the ends of the K—wires that protruded through the cast remains undetermined. Recent evidence (97) indicates that mechanical motion of a percutaneous wire can produce an osteogenic response.

In 1979, a corrected success rate of 84% was reported in a

series of 168 patients, 72% of whom had had previous surgery (94). The use of technitium was developed to help identify patients that had developed synovial pseudarthroses, and who hence were not suitable candidates for the DC stimulation procedure (the synovial pseudarthrosis rate was about 6%). In 1981, a success rate of 79% in a series involving 189 nonunions was reported (95). Comparable results were found by 12 participating investigators (72% of 80 nonunions healed) (95).

In the final series involving 478 nonunions, the average uncorrected healing rate was 66% (96). This series included all patients treated with direct current, including those treated early in the study when the technique was initially being introduced into the clinic, with no patients having been lost to follow—up. The healing rate of the tibia, the most frequently represented bone in the series, was 72%, and the lowest rate of healing occurred in the humerus (33% of 45 bones treated). From an analysis of the failed cases, a series of practical clinical considerations was identified that, if followed, significantly improved the healing rate.

DISCUSSION

CHARACTERIZATION CF ELECTRICAL OSTEOGENESIS

Electrical osteogenesis (EO) is the production of ortho—topic bone by use of electricity —— for purposes here, electrode—delivered electricity. In a typical ED study, a bone lesion is created, and electrodes are placed in the bone. The lesion itself, chemical activity of the electrodes, and mechanical motion of the electrodes each produce an osteogenic stimulus. An acceptable imputation to electricity alone of a causative role in the bone growth must involve suitable controls for these stimuli, and it is this additional amount of bone that is properly described as being caused by electricity.

The existence of electricity—produced bone can be established by quantitative morphometry (73), which is a technique that determines the amount of new bone in a standardized histological plane (93). Since EO promotes callus formation (66—69), mechanical testing in three—point or four—point bending is also

a useful quantitative method for characterizing electrical osteogenesis. Additional callus often stiffens and strengthens healing bone (65). The technique of qualitative histology consists of subjectively characterizing the histological appearance of the treatment site in terms of an arbitrary numeric scale (99). The method is useful if the animal model is such that the DC current does not cause both osteogenic and osteolytic changes (71,73). Attempts have been made to assess EO using radio tracers such as strontium and technetium (62,71) but without significant success because radio tracers do not precisely delineate any particular stage in bone healing (100). Analysis of X–rays, either densitometrically (76) or more typically by subjective evaluation (61) is frequently incorporated into EO studies, but historically it has not proved useful for quantifying electrically produced bone.

Many parameters such as current density, frequency or repetition rate, polarity, and electrode metal can affect electrical osteogenesis, but the dominant influences are exerted by the magnitude and duration of the current. In actuality, for no discernible reason, most animal studies have involved 10–20 days duration of treatment, and most human treatments have involved 84 days. Consequently, current strength emerged as the experimentally important variable. There is broad agreement in the literature concerning the effects of magnitude of current on electrical osteogenesis in animal systems and patients: below 1–5 μA, either no response or only a minimal response is observed; at 5–20 μA, a maximum EO response occurs, accompanied by only a minimal osteolytic response. Above 20 μA, the relative importance of the stimulation and destruction effects of electricity are progressively reversed —— by 100 μA, destruction of bone is the completely dominant process.

Polarity is a relatively unimportant factor in EO produced via inert electrodes such as platinum (75–79). When active electrodes are used (such as stainless steel) the anode decomposes and liberates ions into the tissue. Stainless–steel anodes are not suitable for use in bone (73), and chemical toxicity of the electrode material is probably the underlying reason.

Alternating–current (AC) signals —— usually chosen to mimic an hypothesized endogenous signal —— of various types have been

TABLE 1. Comparison of the Effectiveness of Pulsed vs. Constant Current (20 μA) in Stimulating an Osteogenic Response in the Rabbit Medullary Cavity (81). N = 5—7 in each group. Total charge associated with control current (DC), 36.3 coulombs.

PULSE FREQUENCY (Hz)	CHARGE (coulombs)	PERCENT MEDULLARY CAVITY FILLED WITH NEW BONE	
		Pulsed Current	Control Current (DC)
10	0.36	2.8±0.8*	17.8±1.7*
50	1.8	3.5±2*	19.8±1.2*
100	3.6	5.2±1.2*	19.9±2.1*
200	7.3	6.8±1.5*	20.6±1.6*
500	18.1	12.1±2.1	18.8±3
750	27.2	13.3±0.7	16.9±1.8

$P < 0.001$

employed to stimulate EO, but none has successfully demonstrated any advantage of AC over DC. The present evidence indicates that EO is related primarily to total charge passed through the electrodes, and consequently to signal repetition rate (Table 1).

Bone growth caused by electricity is reparative in nature, and consists initially of intramembranous woven—bone trabeculae that ultimately become remodeled and replaced by lamellar bone as occurs with any other injury. There exists no electrically specialized bone cell (74).

CLINICAL APPLICATION

The question of the clinical utility of EO involves three distinct issues, each of which requires its own methodological approach. One issue involves consideration of whether a therapeutic phenomenon occurred as a result of the treatment that employed EO. Every clinical course of treatment involves many factors such as immobilization, drugs, physical therapy, and

patient motivation, and each factor obviously has some role in the overall result. Without attempting to apportion percent success among various factors in a treatment regimen, one may validly ask whether a particular regimen that employed EO produced a degree of success greater than that produced by a regimen not using ED. Ideally, this issue is addressed by a prospective clinical study in which the use of EO is controlled by the inclusion of a group of patients receiving standard therapy. A distinct issue, one that frequently cannot be addressed because of ethical or practical considerations, is whether a specific factor in a treatment regimen produces a therapeutic result —— that is, its inclusion is associated with a higher success rate than its exclusion, all other factors remaining constant. This issue can be addressed experimentally only by controlling for the putatively responsible factor. Thus, electrodes would be implanted in two groups of patients matched for all pertinent characteristics, but electricity would be applied in only one group and all other aspects of treatment would be identical in the two groups. Under these conditions, a higher success rate in the stimulated group could properly be attributed to the use of electricity.

The third, and most difficult issue, involves consideration of the clinical value of the contemplated treatment. A determination of value comes about as a result of the exercise of clinical judgment. As I have observed the process, ideally it proceeds in the following manner. The clinician considers data provided by a controlled clinical study and weighs the percent success associated with the new therapy against that provided by the standard therapy. A second, distinct, weighing involves the morbidity and convenience of the two courses of treatment. The clinical judgment of value comes about as a kind of overall weighing. If the new therapy is only as good as standard therapy, it will likely have only minimal value unless it is significantly more convenient or results in significantly less morbidity.

Figure 2 depicts an idealized time course of healing of a fracture. The pivotal point in the process is the time at which the injury is judged to be clinically healed. At that point immobilization devices can be removed, and the patient can return to a relatively normal lifestyle. A treatment that safe—

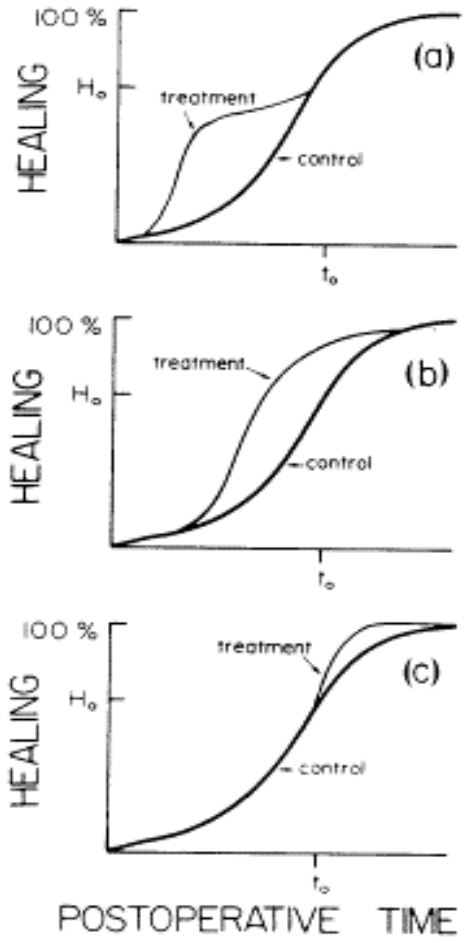

FIGURE 2. Hypothetical healing curve for a fracture. The treatment results depicted in (a) and (c) are not clinically useful. H_0, clinically significant degree of healing; to, post-operative day corresponding to H_0.

ly shortens time to clinical healing (Figure 2b) may have value. If the treatment produces an effect on healing only before (Figure 2a) or after (Figure 2c) the occurrence of clinical healing, it is unlikely to have clinical value —— irrespective of whether E0 actually occurred.

Jorgensen showed that a particular combination of AC and DC current hastened the time to clinical healing in patients with tibial fractures (88). Since the control patients also had transtibial pins, but no electricity, the aspect of the therapy that produced the increased healing can properly be attributed to the E0. The clinical value of Jorgensen's treatment however is dubious for at least two reasons. A significant effort is required to maintain the integrity of the electrical circuitry, and the degree of effort may not be warranted by the degree of the effect produced. Also, Jorgensen's technique likely involved some morbidity as a result of corrosion at the transtibial (presumably stainless—steel) fixation pins which served as electrodes.

Masureik and Ericksson, in their controlled study of patients with jaw fractures, used platinum electrodes thereby eliminating the morbidity associated with corrosion (89). But it is not clear whether electrodes were also placed in the control patients. Thus, although a therapeutic effect was demonstrated, it cannot unambiguously be attributed to the E0. The existence of a therapeutic effect and the absence of morbidity due to electrode corrosion are factors supporting clinical use of the technique. The degree of patient compliance required to maintain the integrity of the electrical connections is a factor tending in the opposite direction.

Sustained efforts using EO in the treatment of nonunion have cone from two groups (96,101). When EO via a titanium electrode was combined with surgical notching of the treated bone, and a hone graft, therapeutic results were demonstrated in an uncontrolled study (101). But there is no data by which to determine the element of the procedure that gas responsible for the result —— perhaps it was the EO, perhaps not.

The nonunion studies of Brighton et al. were also uncontrolled against concurrent conventional therapy. But their patient population was sufficiently well characterized to permit a reasonable comparison with historical controls (96). On that

basis, the conclusion that the treatment provided resulted in a success rate at least equal to that of bone grafting seems justified. A closer issue is that of the component of the therapy that was responsible for the success. Immobilization, drilling through bone, and mechanical stimulus to the treatment site via the relatively stiff electrodes may have, either singly or in combination, significantly contributed to the observed success rate.

Whatever the exact causative factors, the therapy produced a result comparable to that obtained with standard therapy (bone grafting), and with less morbidity than standard therapy (because the percutaneous insertion of the electrodes is less invasive than the full surgical procedure involving the harvesting and transplanting of autologous cancellous bone). The major shortcoming is the relatively high degree of patient compliance required for successful treatment. It seems to me that this factor has mitigated against the clinical value of the technique, thereby accounting for its relative lack of clinical popularity. If the duration of treatment could be shortened however, clinical judgment about the value of the technique might be vastly different.

MECHANISMS

The literature is essentially silent on the question of the specific factor at the cellular level that causes EO. For many years Brighton has intimated that EO was caused or in some manner associated with a relative lack of oxygen in the vicinity of the bone—forming cells (102—104), but the data is weak (103), and the counter—argument is persuasive (105).

There is probably no specific mechanism for the production of EO (106), any more than there is a specific cell by which it is brought about. When Küntscher placed a rusty iron wire in the medullary canal of femurs in dogs, florid callus formation ensued (19). Inflammatory agents such as croton oil also produced extensive callus formation. When large segments of the ulna in dogs were removed, thereby suddenly increasing the forces borne by the radius, it exhibited sudden and dramatic callus formation, thereby increasing its effective cross—sectional area (107). The application of heat also produced callus formation (108).

It seems likely that any somatic stimulus delivered to the bone—cell system results in a common—pathway signal that ignites osteogenesis, and that electricity produces essentially the same effect as do the more prosaic stimuli. The response consists of bone callus composed of woven hone, and demonstrates both an intensity threshold (below which no effect is produced) and a maximum reparative response (above which bone is destroyed, not produced). It proceeds via activation of resting osteoblasts and stimulation of osteoprogenitor cells, and occurs within 24 hours following delivery of the stimulus (11,109). The precise nature of the common—pathway signal actually present at the cell membrane is almost as obscure today as it was when Yasuda first considered the problem 30 years ago.

ENDOGENOUS ELECTRICAL SIGNALS FROM BONE

There are at least three endogenous electrical signals associated with bone. The piezoelectric signal is produced when mechanical forces are applied to bone in such a way as to cause shear along the collagen fibers (24). The piezoelectric signal is not ordinarily manifested in bone containing a normal moisture level because the signal is immediately neutralized by the motion of free charges in the fluid bathing the bone surface. In contrast, streaming potentials can only be measured in moist bone. They arise from the motion of charges in the diffuse layer near a bone—solution interface (38). SEPs are slowly varying electrical potentials that can be measured on the surface of bone, or on overlying tissue. The data presently available is insufficient to establish their origin or their significance in bone physiology.

One of the most fascinating, but unanswered, questions in bone bioelectricity is whether piezoelectricity or streaming potentials (or both or neither) should be identified with the feedback signal that regulates adaptive remodeling. Pollack has presented pertinent data regarding The importance of streaming potentials (59). He measured the potential manifested by moist bone across its cortical thickness when it was mechanically loaded at 1 Hz. The potential gradients were radially directed, and were correlated with osteonal structure: the potentials changed sign depending on whether the osteon was in tension or compression. But, to me, an even more impressive correlation

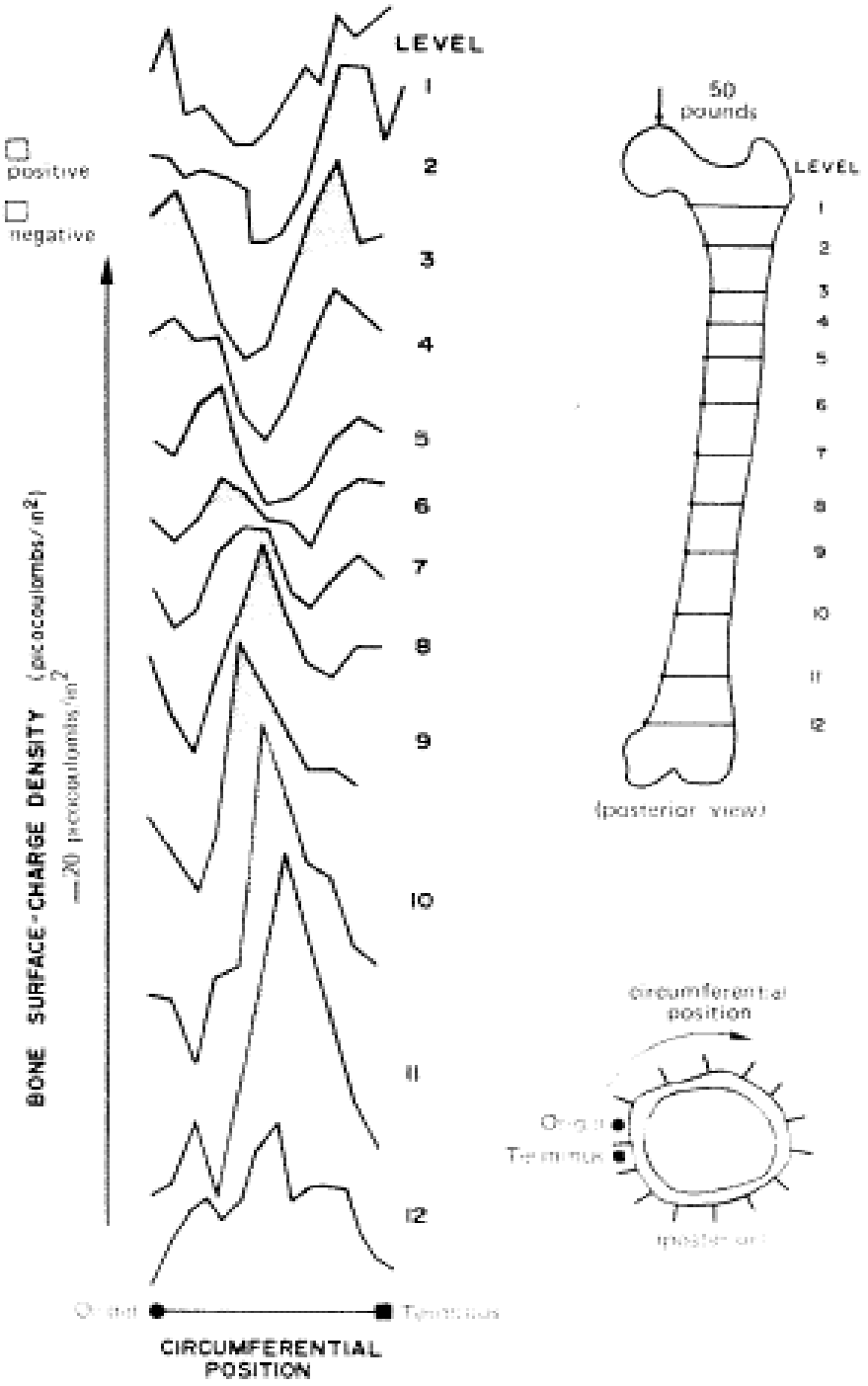

FIGURE 3. Piezoelectric surface–charge density as a function of circumferential position at the indicated levels (49).

between bone anatomy and mechanically—generated electrical signals is contained in McElhaney's data (49). He measured the surface charges that appeared on the surface of a human femur and, as described above, I previously reported a correlation between the measured charges and adaptive remodeling of the femoral outline (50). In his original publication, McElhaney also reported circumferential measurements of the charge density at specific levels of the bone, and this data (which I had not previously analyzed) is displayed in its entirety in Figure 3.

Assume that bone is deposited on areas exhibiting a positive charge, and resorbed on areas exhibiting a negative charge. Further, assume that the amount of bone deposited is directly proportional to the magnitude of the charge. Under these assumptions, McElhaney's data indicates the following adaptive response of the femur to the applied load. At levels 1—4 bone deposition occurs on the medial side, and resorption on the lateral side. At levels 5—7 the pattern of bone growth on one side of the bone and resorption on the other side continues, but the side of the bone exhibiting growth rotates clockwise (viewed from above), so that by level 7 growth occurs only on the anterolateral face. Thereafter, a consistent pattern of change occurs at levels 8—12 in which bone growth occurs on the lateral side of the bone, and resorption on the medial side. The amount of bone growth is greatest at levels 10—11.

Future studies will determine the limits of such an interpretation of electromechanical data from bone. Do long bones loaded non—physiologically generally yield a coherent remodeling response employing the listed assumptions linking surface charge, magnitude, and polarity with bone—cell activity? If 100 microns of the bone surface is removed, the piezoelectric surface charge is dramatically altered (60). All areas of such a free surface were never simultaneously in direct contact with bone cells, and therefore should lack the structural organization to be capable of eliciting an adaptive response.

A NEW BASIS FOR THE CLINICAL USE OF DC CURRENTS

The chronically administered factors associated with beneficial effects on bone growth characteristically function by

triggering bone's plasticity principle —— orthodontic movement of teeth and straightening of malunited fractures are good examples. In contrast, electricity produces a reparative response which is a fundamentally different process from adaptive remodeling. There is no established scientific rationale for chronic administration of DC current to produce EO. Typically, chronic irritants are actually inimical to healing. Perhaps EO produced by chronically administered electricity is a net result of overlapping acute reparative responses (73) or is a response principally manifested only after cessation of stimulation (96). This idea leads to consideration of the initial cellular events following injury, and how DC current might be profitably used to enhance these events.

The initial cellular event after delivery of a stimulus to bone is the activation of osteoblasts lining the bone surface. The osteoblast pool existing prior to the injury is supplemented by mitotic activity from the osteoprogenitor cells, followed by differentiation of some of the daughter cells. Useful data regarding this process has been given by Tonna and Cronkite

The femurs of 5—week—old mice were manually broken, and the extent of the periosteal cellular response was monitored for up to 14 days by flash labeling with tritiated thymidine one hour before killing (a technique that provides a measure of cells undergoing mitoses within one hour of the time at which the label is given) (11). The labeling index (percent of periosteal cells exhibiting the label) in the controls remained at about 2% throughout the post—fracture period. In the fractured animals, a response initially occurred at 8—16 hours after fracture, and peaked at 1—3 days (Figure 4a). The labeling index exhibited a sustained activity of about 10% (5 times more than the activity seen in the controls) during days 4—14. With 18—month—old mice, the maximum labeling index occurred at 4—5 days after fracture (111) (Figure 4b). Thereafter, the labeling index averaged about 6% over days 6—14 (about 30 times the level of the controls).

In another study (112), 5—week—old mice received femoral fractures on one side and O.25—ml injections of either whole blood, serum, or saline into the soft tissue above the periosteun of the (intact) contralateral femur. The injected substances

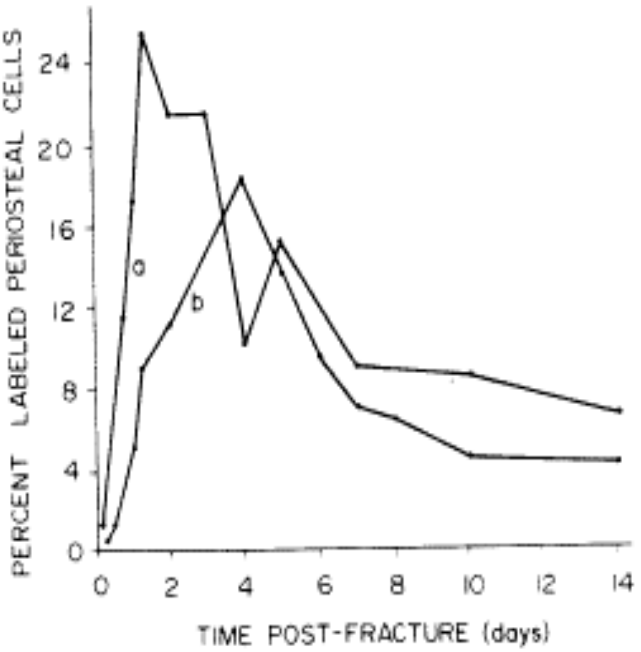

FIGURE 4. Uptake of tritiated thymidine by mice periosteal cells following fracture. Mice aged 5 weeks and l8 months in (a) and (b), respectively (11,111).

produced identical increases in labeling of about 9% (compared to 1% background); the labeling index in the fractured legs was about 16%.

It seems reasonable to assume that, all other things being equal, more bone will be built per unit time when more osteo—blasts are present. The mitotic activity of the osteoprogenitor cells and the extent of differentiation of their daughter cells are the two interrelated factors responsible for the production of new osteoblasts. The number of new osteoblasts, B, on the n^{th} day after an acute injury stimulus is

$$B = \sum_{n=1}^{N} a_n \left(1 - a_{n-1}\right)! \left(L_n + 1\right)! P$$

where a_n is the fraction of osteoprogenitor cells that differentiate on the nth day ($a_0 \equiv 0$), L_n is the labeling index on the n^{th} day, and P is the number of osteoprogenitor cells present at the time of the injury. Employing Tonna's data for the first 4

days following fracture in the younger mice (Figure 4a), and assuming that $a_1 = a_2 = a_3 = a_4 = 0.2$, we find that the osteoblast population is increased by 23%, 23%, 22%, and 19% of the initial osteoprogenitor pool on successive days. If $a_1 = a_2 = a_3 = a_4 = 0.8$, the corresponding increases are 94%, 23%, 6%, and 1%. Thus, the number of new osteoblasts is a result of a complicated interplay between the rates of labeling and differentiation. Any factor that increases L_n and does not alter a_n produces an increase in osteoblasts on the $(n+1)^{st}$ day.

Because electricity is a reparative—eliciting stimulus, it too must result in a cell proliferative response similar to that reported by Tonna —— but in the absence of a bone lesion. In this view, some factor or combination of factors associated with the actual inflammatory reaction to the current —— exudation of leukocytes, activation of tissue enzymes, temporary tissue hypoxia are possibilities —— serves as the link between the stimulus and the activity of the osteoprogenitor cell. Furthermore, the osteoprogenitor response as determined by the labeling index is, in some sense, proportional to the extent of the injury (the response to a fracture was almost twice that of the response to O.25—ml injections (112)).

Based on these considerations, I conclude that bone healing (or augmented bone healing) can be brought about by acute administration of DC current above some appropriate threshold to produce a pulse increase in the number of new osteoblasts, followed by a second (and possibly subsequent) doses of DC current at a time when the initial increase in mitotic activity has abated.

In a preliminary test of this idea, bilateral slot osteotomies (7 x 2 mm were performed in rabbit mandibles and a stainless—steel electrode was attached to the hone and brought out through the skin in the area of the ramus (114). A current of 20 μA, negative polarity, was applied to one side, 4 hours/day for 2-4 days, and the other side served as the control. The extent of bone growth into the slot at 8 days after surgery was assessed qualitatively, and it was found that significantly more bone was present in the slot on the stimulated side in animals treated for 2-4 days. In animals stimulated on one side for the entire 8-day post-surgery time period, no bilateral differences in healing were observed (114).

These observations did not involve quantitative measurements of bone formation, and therefore must be regarded only as preliminary observations. In addition, an effect on the rate of fracture healing manifested as quickly as 8 days after surgery is unlikely to have clinical significance because it probably occurs at a time prior to clinical healing. Despite these limitations, the observation lends some support to the analysis of the existing literature given above.

The possibility that relatively brief stimulation delivered to an injury site during the immediate post—injury period (perhaps up to a week) actually enhances healing might significantly alter present evaluations of clinical value of EO. During an open reduction of a fracture an electrode could be placed directly over the periosteum or in the bony defect. The DC current could be administered with external equipment during the period of hospitalization, and the wire could be removed prior to discharge as would be the case with any other temporary indwelling device. If the DC current recruits additional osteo—blasts in the absence of creating additional damage, and if the additional increment of bone produced adds stability more quickly, then the functional result would be accelerated healing. This process would not involve the basic step of direct communication with bone cells; instead, the effect of the DC current would be transduced to the common—pathway signal that triggers osteoprogenitor—cell mitosis. One advantage associated with providing a stimulus that does not function at the basic level of communicating directly with osteoprogenitor—cell membranes is that the danger of sending the wrong signal is proportionately reduced. That is, since the osteoprogenitor cell itself is not presented with a novel artificial environment, there seems little basis for concern about the possibility of triggering undesirable neoplastic growth (115).

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