Calcif. Tiss. Res. 26, 93-97 (1978)

Calcified
Tissue Research

Review

Electrical Osteogenesis—Pro and Con*

Robert O. Becker

Orthopedic Section, Veterans Administration Hospital, and Department of Orthopedic Surgery, SUNY Upstate Medical Center, Syracuse, New York 13210

The interest in electrical osteogenesis (EO) has increased exponentially over the past decade; a recent review (1) listed 119 publications dealing strictly with electrical stimulation of bone growth. Because of its obvious clinical implications, I believe it is important to critically evaluate this technique, in regards to efficiency, safety, and mechanism of action. At this time the weight of the evidence, gathered both from laboratory animal and clinical studies, indicates that electrical forces can stimulate bone growth (1). The prime question then becomes, how does it work? Implicit in the answer to this question are answers to the questions of safety and most efficient technique of application.

Before discussing the artificial stimulation of bone growth, it is wise to consider the types of growth normally exhibited by bone. There are, of course, three major types: epiphyseal plate growth in length, appositional growth in response to mechanical stress, and growth following fracture. The cellular mechanisms involved in each one are quite different, and there is no reason to believe that the same biological mechanism is at work in all three. Significantly, all of the reports dealing with EO in the literature are concerned with the last type, fracture healing. This growth process is characterized by direct osteogenesis from the periosteum and by the appearance of a mass of primitive cells in the medullary cavity, which subsequently undergoes mitosis followed by differentiation into cartilage and bone. From the viewpoint of the biologist, this medullary growth process is an example of regeneration, being characterized by the appearance of a primitive blastema (the clinician's "callus"). Indeed, this is the only truly regenerative growth process still available to man; other so-called regenerative growth processes in man lack this crucial blastema phase. Not only do the majority of published reports on EO deal with fracture healing, but they deal specifically with this intramedullary blastema formation. Biologically, then, EO is the electrical stimulation of a normal regenerative growth process. Historically, the roots of EO lie in regeneration research and a useful perspective may be gained by briefly reviewing the events that led to the present clinical applications.

Despite the knowledge of this process in antiquity and the work of many investigators, the mechanisms stimulating regenerative growth were totally unknown until 1945 when Rose (2) described a possible "threshold" relationship between the extent of injury and regenerative growth. His observations were confirmed by Polezhaev in the following year (3), and both investigators were able for the first time ever to restore a modest amount of limb regeneration to an animal normally lacking this ability (adult frog) by increasing the extent of trauma. In the next decade, Singer (4) established the existence of another threshold factor, the extent of

Send offprint requests to R.O. Becker at the above address.

*On occasion, the *Editorial* category of the journal will be replaced by a *Review* of a topic considered by the Editor-in-Chief to be both timely and provocative.

0008-0594/78/0026-0093 $01.00

nerve supply. He also was able to obtain a modest amount of limb regeneration in the same species, by increasing the nerve supply to the limb. In 1958 I reasoned that two such disparate factors as trauma and innervation must be working through a common mechanism. It was known at that time that both trauma (5) and innervation (6) had a similar direct relationship to the current of injury. The current of injury is the appearance of a measurable direct current electrical potential and current at any site of injury in any living thing. Although it had been largely considered by science as an insignificant second-order phenomenon, I decided to measure the difference in the current of injury in two closely related species, one a regenerator, the other not. A major difference was found and when the data were presented at the AAOS meeting in 1960, it was also postulated that at least one controlling factor in regenerative growth was the production at the site of an appropriate electrical environment (7). Over the years since then, we have been able to show that the local current of injury was an expression of a total body electrical data transmission and control system, associated with some element of the central nervous system. Following up on our observation, Smith (8) succeeded in 1967 in securing the same amount of limb regeneration in the frog as Rose, Polezhaev, and Singer, by implanting a small electrical device. By slightly altering Smith's device, we were subsequently able to obtain limb regeneration in a mammal for the first time (9). In this experiment, rat forelegs were amputated at the mid-humeral level, subsequent electrically stimulated regrowth included the distal humerus complete with elbow joint with all the necessary diverse cell types including a normal epiphyseal plate and all adjacent soft tissues. In 1974 Smith (10) reported the successful regeneration of an anatomically complete total foreleg in the frog by implantation of a battery-operated device. Most recently Rose (11) reported on a series of experiments conclusively identifying the nerve factor responsible for regeneration as the electrical potential generated at the site. Thus since 1960 it has been possible to positively identify at least one of the significant factors responsible for regenerative growth as the production of an appropriate electrical environment at the site of injury. We presently believe this is generated by a specific electronic system associated with the nervous system which controls a variety of primitive functions including growth and repair (12, 13).

While these basic investigations on regenerative growth in general were being pursued, we were also involved in a study of the electronic solid-state properties of bone and their functional significance. To fully understand EO, it is necessary to integrate these two lines of endeavor and hopefully to correct some misconceptions that have become prevalent.

Shortly after the presentation of our original observations in 1960 on the relationship between the current of injury and regeneration, we began, in conjunction with Andy Bassett, a study on the possibility of the stress piezoelectric effect in bone. We found that bone does exhibit such a phenomenon (14) and were subsequently able to identify the bone collagen as the generating source with the signal being rectified at the PN junction formed between the collagen and the apatite mineral (15). This rectified signal is directly proportional to the important parameters of any mechanical stress applied to the bone, and we have subsequently been able to relate this piezoelectric effect to bone growth in response to such mechanical stress (14). In this light, bone may be viewed as a true cybernetic self-organizing system, but only in regard to Wolff's law proper. It is most important to indicate that the electric signals arising from the piezoelectric effect in bone are quite unlike those observed in regenerating tissues. The regeneration signal is a slowly varying direct current (DC) extending from the time of injury until healing is complete and dependent on the integrity of the nerve supply. The piezoelectric signal is a single pulse, of short duration, occurring simultaneously with the application of mechanical stress and immediately decaying. It results from specific properties inherent in bone and is not neurally dependent. In the mid-1960s, therefore, Dave Murray and I began a study of fracture healing itself as a regenerative phenomenon. Using the bullfrog tibia, we found that the pattern of electrical potentials from the time of fracture until healing occurred closely resembled the regeneration sequence (16). Most importantly, we identified the cell type responsible for the blastema (callus) formation as being the nucleated erythrocyte, which is the normal circulating red cell in all animals except mammals. In the fractures studies, the red cells in the fracture hematoma underwent rapid dedifferentiation to form the blastema. This afforded us an unparalleled opportunity for a crucial experiment. If the electrical factors observed at the fracture site were in truth the trigger for the cellular processes of healing, then exposure of the normal nucleated red cell to the same electrical factors artificially generated in vitro should produce dedifferentiation. We were subsequently able to observe morphological changes of dedifferentiation in vitro with application of electrical currents and voltages simulating those measured at the fracture site (17). In later studies, we measured appropriate changes in DNA, RNA, and protein composition in these cells (18). The circle is now

completed; the trauma of the fracture triggers the neural electrical control system into action producing the appropriate DC electrical environment, which in turn produces the cellular transformations necessary for the blastema formation. The electrical signal persists for a pre-set period of time, slowly decaying until healing is complete. In this concept, an adult type nonunion is a situation in which, for some reason, the cellular processes have not resulted in junction between the fragments and the control system has reverted to the quiescent state. This observation not only seemed to conclusively establish the role of electrical potentials in fracture healing, but it also enabled us to study and determine with precision the optimum electrical environment required to produce the cellular stimulation. It was found that in vitro, an effective DC range existed, with both upper and lower limits (currents below 1pA/mm^2 and above 1000 pA/mm^2 were ineffective in producing cellular transformation). The optimum current level was 300 to 500 pA/mm^2 and short duration pulses were ineffective in producing cellular changes. These in vivo observations were then the basis for our subsequent experiments on the electrical stimulation of limb regeneration in the mammal and ultimately the guidelines for our clinical studies on EO.

At the present time we have found that levels of direct current of 100 nA/cm of implanted pure silver electrode, as the cathode, are effective in producing osteogenesis in the immediate vicinity of the electrode, where the current density would be approximately the same as on the electrode (19). Increasing the current per centimeter results in the zone of osteogenesis moving away from the immediate vicinity of the electrode. Since the current density would decrease with distance, we interpret this to indicate that osteogenesis occurs in that area where this factor is optimal. Since this current density is close to that determined as the optimum range for amphibian erythrocytes, we propose at this time that there exists a range of current density for direct cellular stimulation in the osteogenic system, with both upper and lower boundaries. How can this be reconciled with a number of literature reports indicating osteogenesis from current densities an order of magnitude higher (20)? Analysis of the literature coupled with experiments in our laboratory has led to the conclusion that if current densities are arranged on a continuum from the lowest to the highest, a relatively narrow zone in the low densities is osteogenic by virtue of a direct stimulatory effect on a sensitive cell population. This zone of osteogenesis is followed by a zone at slightly higher current densities in which a number of negative reports—failure to secure osteogenesis—are listed. This negative zone is followed by a zone of increasing current densities in which osteogenesis is reported (21). By duplicating in vivo the higher current techniques, we found that all were producing low to moderate levels of electrolysis. Since bone is known to grow in response to irritation, the electrochemical changes produced by this electrolysis are proposed to be the irritative stimulus to osteogenesis in this region of current densities. One now is faced with a choice between a low biologically significant level of stimulation and a high irritative level of stimulation. Although on theoretical grounds it would appear that the choice is obvious, we must be careful not to so exclude techniques that may offer many advantages. At this time, no definite answer can be given in regard to relative safety and efficiency of low versus high current techniques.

A problem inherent in the implanted electrode, direct current stimulation technique that has been largely ignored is the composition of the electrode. The concept that a metal, clinically inert in standard practice, would be similarly inert when it was passing electrical current in vivo is just not correct (22). There are major electrochemical differences among electrodes of different materials even when operating at the same potential. We originally chose 99.99% pure silver as our electrode material based on its lower interfacial resistance in vivo. We reasoned this would permit higher currents at lower voltages, and since electrolysis is largely a voltage phenomenon, it would provide a margin of safety not available with other metals. Since our work began, we have discovered another advantage of this material. Silver ions have an extremely broad spectrum of antibacterial activity and, at the same time, extremely low toxicity for mammalian cells. When a silver electrode is used as the anode, it emits into the surroundings silver ions unaccompanied by any corresponding anion. We have found that these silver ions will penetrate approximately 1 cm of tissue, within which they will exhibit a bactericidal action on gram-negative as well as gram-positive bacteria, both aerobic and anaerobic in type. Details on the clinical use of this technique in osteomyelitis with and without nonunions are presently in press (23).

In summary, we are presently using pure silver wire electrodes inserted directly into the nonunion site, operating as the cathode at 100 nA/cm of exposed wire with voltage supplies limited to not more than 0.9 V. In this technique, we are not only within the biologically significant zone of current density, but are also certain that we are not producing harmful effects. Should it be desirable, the same electrode can be operated as the anode, exerting a bac-

tericidal effect over a 1 cm distance, for as long as 48 h with no inhibition of subsequent osteogenesis when returned to the cathode polarity. I must caution that I do not yet consider this to be the optimum technique and I do believe that one of the most urgent tasks before us in further evaluating this technique is that of a systematic study of electrode electrochemical reations in vivo.

This leads us naturally to a consideration of Bassett's present work based on the concept of inducing an appropriate electrical environment in tissues by exposing them to a pulsed magnetic field, obviating the need for implanted electrodes. Although a pulsed field will certainly induce potentials in the tissues, it is quite doubtful that they will have much similarity to those derived from implanted electrodes operating at DC. Nevertheless, he has reported experiments on animals in which acute fractures healed at a faster rate (24) and clinical studies involving both adult type nonunions and patients with congenital pseudarthrosis of the tibia with good results (25). We were able to try various models of his device on a small number of our adult type nonunions. Unfortunately, in our small series we were unable to obtain either a satisfactory clinical result or any evidence of cellular stimulation as judged by radiography or technicium polyphosphate bone scans. However, I have had the opportunity to review a number of Bassett's results with congenital pseudoarthrosis of the tibia, and in those there was no doubt that not only did union occur, but in fact, there was restoration of the normal tibial profile. At this time, lacking further firm evidence, we believe Bassett's technique is acting directly on the electronic control system in the peripheral nerves and not on the osteogenic cell pool proper. In this view, his animal experiments with fresh fractures may be viewed as the field enhancing an already active electronic control system. It is well known that congenital pseudarthrosis has a large neurological component, and we postulate that in this instance the fields are replacing some functionally inadequate component of DC system operation. Failure to produce osteogenesis in adult nonunions with quiescent healing control systems would then be expected. Obviously, these concepts are theoretical; however, they are quite amenable to experimental study. One of Bassett's recent proposals reportedly deals with the widespread application of his technique to fresh fractures in the human population, with the aim to secure union at an earlier time than normal. In my opinion, there are several aspects of this proposal requiring considerable cogitation. First, the artificial acceleration of a complex cellular activity involving dedifferentiation and mitosis may well carry a risk of neoplasia. Second, although the biological effects of applied electromagnetic fields are just beginning to be understood, it is known that they are subtle and that a number are harmful (26). I believe great caution should be exercised before considering this widespread application for a clinical condition that resolves satisfactorily in the great majority of cases.

It is my view that electrical osteogenesis is a real phenomenon, with immediate clinical utility in the problem case. Further experimentation is required, particularly in the areas of electrodes and techniques. Until this is completed and a judgment made of the optimum method, I believe its use should be restricted to those cases in which the risk-benefit ratio would be favorable, considering that the risks involved may not become apparent until further clinical experience is gained.

Our concept of it as a restarting of a regenerative growth process in man has implications beyond its present and immediate applications. Our demonstration of electrically stimulated limb regeneration in mammals implies that the same technique may possibly be used to produce regeneration of organs and tissues in man. In the orthopedic area, we have already demonstrated electrical stimulation of hyaline joint cartilage in mammals (27) and have obtained partial regrowth of resected humeral heads in the laboratory rat. Much more work remains to be done; however, I believe that many will share my view that these techniques may well be ushering in a new era in clinical medicine.

Acknowledgment. This work was supported by the Veterans Administration Research and Development Service.

References

1. Spadaro, J.A.: Electrically stimulated bone growth in animals and man, Clin. Orthop. **122**:325–332, 1977
2. Rose, S.M.: The effect of NaCl in stimulating regeneration of limbs of frogs, J. Morpholol. **77**:119, 1945
3. Polezhaev, L.W.: The loss and restoration of regenerative capacity in the limbs of tailless amphibians, Biol. Rev. **21**:141, 1946
4. Singer, M.: The influence of the nerve in regeneration of the amphibian extremity, Q. Rev. Devl. Biol. **27**:169, 1952
5. Matteucci, C.: Surle courant electrique de la Grenoville, Ann. Chim. Phys. **68**:93, 1838
6. Zhurmunskii, A.V.: On the parabiotic nature of the reaction of mammalian skeletal muscles to denervation, Fiziol. Zh. **44**:577, 1958
7. Becker, R.O.: The bioelectric factors in amphibian limb regeneration, J. Bone Joint Surg. **43-A**:643–656, 1961
8. Smith, S.D.: Induction of partial limb regeneration in *Rana pipiens* by galvanic stimulation, Anat. Rec. **158**:89, 1967
9. Becker, R.O., Spadaro, J.A.: Electrical stimulation of par-

tial limb regeneration in mammals, Bull. N.Y. Acad. Med. **48**:627–641, 1972
10. Smith, S.D.: Effects of electrode placement on stimulation of adult frog limb regeneration, Ann. N.Y. Acad. Sci. **238**:500, 1974
11. Rose, S.M.: Personal communication.
12. Becker, R.O.: The significance of bioelectric potentials, Bioelectrochem. Bioenergetics **1**:187–199, 1974
13. Becker, R.O.: The basic biological data transmission and control system influenced by electrical forces, Ann. N.Y. Acad. Sci. **238**:236–241, 1974
14. Bassett, C.A.L., Becker, R.O.: Generation of electric potentials by bone in response to mechanical stress, Science **137**:1063–1064, 1962
15. Becker, R.O., Bassett, C.A.L., et al.: The bioelectric factors controlling bone structure. In: Bone Biodynamics, pp. 209–232. Little, Brown and Co., Boston, 1964
16. Becker, R.O., Murray, D.G.: The electrical control system regulating fracture healing in amphibians, Clin. Orthop. **73**:169–198, 1970
17. Becker, R.O., Murray, D.G.: A method for producing cellular dedifferentiation by means of very small electrical currents, Trans. N.Y. Acad. Sci. **:29**606–615, 1967
18. Harrington, D.B., Becker, R.O.: Electrical stimulation of RNA and protein synthesis in the frog erythrocyte, Exp. Cell Res. **76**:95–98, 1973
19. Becker, R.O., Spadaro, J.A., et al.: Clinical experiences with low intensity direct current stimulation of bone growth, Clin. Orthop. **124**:75–83, 1977
20. Brighton, C.T., Friedenberg, Z.B., et al: Clinical experiences for the treatment of non-union with constant DC., Clin. Orthop. **124**:106–123, 1977
21. Marino, A.A., Becker, R.O.: Electrical osteogenesis: an analysis, Clin. Orthop. **123**:280–282, 1977
22. Berger, T., Spadaro, J.A., et al: Orthopedic electrodes: metal and polarity evaluation in short term marrow cell culture. Trans. Third Ann. Meet Soc. Biomaterials, p. 141, 1977
23. Becker, R.O., Spadaro, J.A.: Treatment of orthopedic infections with electrically generated silver ions: a preliminary report, J. Bone Joint Surg. (in pres)
24. Bassett, C.A.L., Pawluk, R.J., et al.: Bone repair by inductively coupled electromagnetic fields, Science **184**:575–577, 1974
25. Bassett, C.A.L., Pilla, A.A., et al.: A non-operative salvage of surgically resistant pseudarthroses and non-unions by pulsing electromagnetic fields, CORR **124**:128–143, 1977
26. Marino, A.A., Becker, R.O.: Biological effects of extremely low frequency electric and magnetic fields: a review, Physiol. Chem. Phys. **9**:131–147, 1977
27. Baker, B., Spadaro, J.A., et al.: Electrical stimulation of articular cartilage regeneration, Ann. N.Y. Acad. Sci. **238**:491–499, 1974

Received June 7, 1978 / Revised August 3, 1978 / Accepted August 3, 1978