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Evaluation of Electrical Techniques for Stimulation of Hard Tissue Growth

VA Hospital
Irving Avenue and University Place
Syracuse, New York 13210
Robert O. Becker, M.D., J. A. Spadaro, Ph. D., and A. A. Marino, Ph. D.

Background

The main thrust of this program has been to determine the factors that stimulate and control growth and healing in the musculoskeletal system, so that clinical applications may be made.

From the viewpoint of basic biological knowledge, several factors were clearly evident when we began our studies in 1958. First, the healing of an injury is a controlled process; i.e., in the normal condition, cellular activity is "turned on" in response to the injury, proceeds until healing is complete, and is then turned off. From this point of view it is a classic example of a feedback control system. Secondly, when the entire spectrum of the animal kingdom is looked at, it becomes apparent that the healing processes of more primitive animals are far more competent than those of the human.

Of particular interest to us is the healing process of regeneration in which a missing portion of the body is regrown into a normal complex structure. The salamander, for example, is capable of regenerating a limb in a few weeks. The structure of the salamander limb is as anatomically complex as the corresponding human limb. Why then is it that we cannot regrow our limbs? The question: What are the factors that stimulate and control regeneration of the salamander limb? would appear to be clinically pertinent. In the human, the only truly regenerative growth that we possess is the healing of fractures: therefore, knowledge of these factors would at least be useful in the treatment of non-unions of fractures in the human. Furthermore, such knowledge may well be put to clinical use in stimulating regenerative growth that we as humans no longer have. Such growth control would be applied not only to the re-

growth of limbs, but more immediately (and more pertinently) to such structures as skeletal muscle, cardiac muscle, peripheral nerve and spinal cord, joint cartilage and total joints in general.

We began our studies in 1958 with an evaluation of a factor previously thought to be unrelated to any control function—the electrical current of injury. This is revealed by an electrical potential which can be measured at any site of injury in any living organism. We found that the current of injury persists throughout the entire time of healing, and that it follows an entirely different sequence of changes in injuries healing by regenerative growth than it does in similar injuries in other, but closely related, animals not capable of regenerative growth (1). The pattern is so striking that it was concluded that the local electrical factors at the injury site represented only a signal resulting from the operation of a control system that permeated the entire organism.

Intensive study was devoted to this issue, and it was determined that these electrical potentials are related to the central and peripheral nervous system where they represent the activity of another mechanism more primitive (than the well known action potential) for the transmission of data. The present concept is that this analog-type data transmission and control system antedates the action potential system, and that it is responsible for a number of primitive functions in addition to growth control. Such additional functions defined so far include; (i) pain sensation, (ii) general level of excitability of the action potential system, and (iii) control over biological cycles. Most recently we have acquired data indicating that this system may be residing in the perineural cells of the CNS, the glia cells centrally, and the Schwann cells peripherally. While numerous papers have been published in this area of neuroelectronics, two recent publications summarize and present the data within the systems concept (2,3).

From a clinical point of view, we were primarily interested in the output of the system that appeared to have growth stimulating and growth controlling properties. Since growth is perforce the result of cellular activity, and since regenerative growth requires not only mitosis, but also a dedifferentiation (a return to a primitive cell type) we directed a study at the results of exposure of cells to various levels of direct current. Our test system was the nucleated erythrocyte, and we found that dedifferentiation did indeed occur, but only in a narrow range of current and voltage of extremely low values (4,5). We were then able to proceed to determine, in detail, the control system that regulates regenerative growth in general and fracture healing specifically (6).

Obviously, the primary question is: With this knowledge, is it

possible to stimulate some measure of regenerative growth in mammals?

In our experiments in 1972, we amputated the foreleg of laboratory rats between the shoulder and elbow and implanted small electrical units designed to produce the appropriate level of current. We obtained gratifying regrowths, occasionally as far as regeneration of the entire distal humerus complete with an elbow joint of normal histological appearance (7,8). In similar experiments which are unpublished, we were able to stimulate considerable regrowth of the proximal humerus, an important point since in this instance, growth is proceeding proximalward. Such "upstream growth" does not normally occur even in animals capable of regeneration.

The first clinical application of this knowledge has been in the area of un-united fractures. Over the past 3 years we have treated a variety of cases with various electrical techniques. We have found that growth can be stimulated solely by appropriate electrical currents and voltages (which must be in the biologically significant range). A recent publication presents all the technical details (9).

Several points must be emphasized at this juncture. First, while all electrical parameters are designed to be well below the level of harmful effects, they are further designed to duplicate, in so far as is presently possible, the values that would have been produced at the time of the original fracture by the patient's own electrical control system. Thus, we are employing a simulation of a natural biological process and not some modality that is foreign to the body.

Secondly, such simulation can only approximate a natural biological process when the electrical parameters are injected by metallic electrodes. The electrochemical events that occur in the immediate vicinity of a metallic electrode passing current are poorly understood for simple systems, and are completely unknown for biological systems. A complete systematic study of these processes is urgently required before the full potential of this growth control process can be clinically realized. We are presently beginning such a study. From an orthopedic point of view, the possible clinical applications have been indicated in a number of publications (10, 11, 12). Obviously other clinical applications can be entertained, ranging from effective pain control to stimulation of bone growth into suitable metallic devices to provide anchorage points for external prostheses.

Most recently we have investigated the possible application of our techniques to situations requiring growth retardation rather than stimulation. Since, biologically, all active growth processes are

characterized by high electrical negativity, we had always employed metallic electrodes (generally silver) driven negatively (cathode) in both animal and human studies. The obvious question then was, would positive potentials retard growth? We found that metallic electrodes, when used as the anode, are very active electrochemically and in general, exhibit a tendency to give off, and drive into the local tissues, metallic cations (a silver electrode will inject silver ions, a platinum electrode, platinum ions, etc.).

Thus, at this time, we have been unable to generate a pure anodal environment without the accompanying electrochemical changes. However, this tendency to emit positive metallic ions from the anode has itself proven to be of very great clinical interest. For example, silver has been long recognized as a potent antibacterial with little, if any, harm to the mammalian cell system. The problem in its clinical use has been that silver compounds either dissociate very little and are ineffective, or they dissociate readily and are toxic. Metallic silver foil is still used frequently by European surgeons as a primary wound dressing; however, the emission of silver ions from it is negligible. We found that silver electrodes, when driven positive, will readily emit silver ions which will migrate along the lines of voltage gradient, penetrating tissues for approximately 1 cm. These are unaccompanied by any new anion and are non-toxic to mammalian cells.

Their anti-bacterial spectrum appears to be complete and we have found no type of bacteria that cannot be killed with this modality.

We have tested this concept clinically in 12 cases of osteomyelitis, with excellent results. It now appears that for local infections, we have an extremely effective treatment modality which can effectively suppress all varieties of bacteria and a number of fungi in tissues with poor blood circulation without damaging the host cells or tissues. A full report is in preparation.

This technique may be used to drive other metallic cations into tissues, although little is known about the resultant effects. We have experimentally applied the concept to one other system—the rheumatoid arthritic synovium. Here it has been known that gold, systemically administered, is effective in suppressing the synovial cell overgrowth. The problem was that the majority of patients exhibited no effect because the gold did not penetrate the affected joint spaces. In animals with experimental arthritis, we found we could effectively suppress the synovial cell overgrowth by inserting a gold wire into the joint cavity and driving it positive, with a current and potential below electrolysis levels, with one treatment or 30 minutes duration. Obviously the gold ions are injected directly

into the desired site and there is no total body burden of gold with its known toxic effects. It would appear feasible to consider further exploration along these lines in rheumatoid arthritis and other conditions, as long as the target cell or tissue to be suppressed was sufficiently different from the normal cells or tissues.

Present Investigations

The laboratory is presently involved in a systematic study of various techniques for the injection of electrical forces into tissues, particularly bone, in an attempt to define the optimal safest method for stimulation of bone growth. We are also involved in a study of the biological effects of electrical fields of various types, to search for beneficial or harmful effects. We also hope to begin a systematic study of a variety of metallic electrode systems in biological tissues to elucidate the electrochemical changes that occur, and to search hopefully for other useful biological effects.

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