# The Control of Healing Processes

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The ability to heal a wound is a basic attribute of all living organisms; certainly, without it, the surgeon could not function. Until the past few decades, the major thrust of orthopaedic surgery was toward the optimal restoration of anatomic relationships and the providing for the optimal environment to permit healing. The techniques utilized depended almost entirely upon the ability of bone to heal itself.

Within the past few decades, we have seen the development of the concept of the replacement of malfunctioning parts by nonliving materials. This has resulted in an increase in our ability to symptomatically treat a variety of pathologic conditions which were previously not amenable to therapy. It is interesting to note that these conditions—degenerative arthritis for example—demonstrate a failure of the bone and associated structures to heal in an optimal fashion. The concept of artificial replacement accepts this fact and obviates it by substituting a manufactured part for the diseased part.

## Mechanistic Thinking

It is not my intention to belittle the very real and important contributions made by joint replacement. Certainly, at the present time it is the procedure of choice in the mid and older age groups. However, its obvious successes have led to the development of a sense of mechanistic thinking in orthopaedic research and practice. It is my belief that orthopaedic surgery, in common with all surgery, rests on a biologic foundation which we ignore at our peril.

Even the most enthusiastic proponent of total-joint replacement would agree that the optimal replacement would be restitution of the joint, in normal configuration, from the patient's own tissues. Recent developments have indicated that this possibility is not as remote as previously thought. We now know that very small electric forces have profound effects on healing processes and that clinical applications of this concept may have important connotations for orthopaedic surgery in particular. I believe that it would be useful at this time to briefly review the general background of this area and then to indicate its specific areas of interface with orthopaedics.

## The Ability to Heal

While the ability to heal is general with all living organisms, it demonstrates an inverse relationship with the phylogenetic scale. Perhaps the crossover point (the organism with the greatest complexity and, in addition, the greatest competency in healing processes) is represented by the tailed amphibians, particularly the salamanders. These are vertebrates and have an antomic ar-

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**Dr. Becker published his first paper on regeneration in 1960 and since then all of his work, both in the biological and biophysical areas, has revolved about the concept of biological growth systems. He has published 62 papers in scientific journals and has presented an additional 72 papers at major national and international scientific meetings. In his most recent paper, he reported the ability to induce regeneration of normal hyaline joint cartilage in mammals and presented details for a new class of prosthetic devices based upon his ability to stimulate regeneration of the patient's own tissues.**

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rangement entirely analagous to that of the human. Many are capable of regenerating an entire limb after amputation. The structure formed is identical to the one removed and of a complexity similar to the analogous human extremity. The salamander, in addition, is capable of regenerating up to one third of the brain and a similar fraction of the ventricular myocardium.

The tailless amphibians, represented by the frog, lack this ability completely in the adult stage, but do possess it in their larval stage (in which they have a tail). The frog has, therefore, been a favorite subject for regeneration research, seeming to be an animal that has progressed in complexity only slightly from the form that was capable of regeneration.

The earliest report of the successful stimulation of partial limb regeneration in the frog was by Rose in 1945, who, following forelimb amputation, exposed the animals to hypertonic saline solution. The following year, the same result was obtained by Polezhaev, who merely repeatedly traumatized the amputation stump with a needle. These results seemed to indicate that, at least in the frog, increasing the amount of trauma stimulated regeneration.

About 10 years later, Singer demonstrated that regeneration was mathematically related to the amount of nerve tissue in the amputation stump, with regeneration occurring when 30% of the total tissue was nerve. Singer also succeeded in stimulating partial limb regeneration in the frog by transplanting functionally intact additional nerves into the extremity. His work indicated that increasing the amount of nerve tissue stimulated regeneration.

A link between these two factors, trauma and nerve, was subsequently provided by Simukhin in 1957, who noted that the current of injury in skeletal muscle was proportional to the extent of innervation of the muscle.

## Injury and the Healing Process

Despite the fact that modern physiologic concepts had relegated the current of injury to a second order phenomenon due theoretically to the injured cell membranes at the site, the sequence of observations related above seemed to indicate that it might play an active role in the healing process. Our laboratory investigated this in 1960 by measuring the time course of the injury potentials at an amputation site from the date of amputation until healing was completed. This was done in a series of normal salamanders who healed by generating a new limb and a similar series of normal frogs who healed by scarification and epithelialization. A marked difference in the current of injury was noted between the two groups (indicating, at least, that this potential was something more than injured cell membranes).

Subsequent work on the relationship between the nerves and the injury potentials revealed that some portion of the nervous system generated and transmitted direct current electric signals which were, in part, afferent—indicating that trauma had been incurred and, in part, efferent, which stimulated local repair processes. The mechanism of generation and transmission appeared to be semiconducting in nature and we evolved the concept that this constituted a primitive data transmission and control system concerned with notification of injury and stimulation of the necessary cellular healing processes. Thus, Singer's neural factor was postulated to be direct current electric phenomena rather than a specific neurochemical. (The fact that Singer found no correlation between the type of nerve, action potentials or any neurochemicals and the regenerative process seemed to substantiate our concept.)

In this light, the gradual loss of regenerative capacity with ascendancy on the phylogenetic scale became understandable. There appears to be a constant ratio between total body mass and total nerve mass in all organisms. Increasing organismal complexity is concomitant with increasing encephalization, with its sequestration of greater and greater amounts of the total nerve mass into the brain. This obviously results in the diminution of the total amount of nerve mass in the peripheral nerve system, with a drop below the threshold necessary to produce adequate electric effects occurring just above the tailed Amphibia. If, however, the nerve factor responsible for regenerative healing is electric in nature, it should be replaceable by externally generated electric forces simulating the amount and type necessary, even if the amount of nerve present is inadequate.

## First Confirmation

The first confirmation of this came from the work of Professor Stephen Smith in 1967. He was able to produce the same amount of partial limb regeneration in adult frogs as was obtained by Rose, Polezhaev and Singer by implanting small bimetallic electric generating sources. This work was extended to the mammals in our laboratory and in 1972 we were able to report the stimulation of partial limb regeneration in laboratory rats by similar techniques. Perhaps more clinically relevant at the present time, we have been able to stimulate major regeneration of articular cartilage in the adult rabbit, again by similar techniques.

It was recognized that the bimetallic devices did not produce the optimal electric environment and, recently, battery-operated devices have been designed by several groups. Smith has recently reported the stimulation of anatomically and functionally complete limb regenerates in frogs by their use, and we have noted the complete repair of major articular cartilage defects in rabbits.

Bone, from the point of view of regenerative growth, is an anomalous tissue. It is the only tissue in the mammal capable of major regeneration — evidenced, even in the adult, by fracture healing. Bone, however, is sparsely innervated (except for the periosteum) and falls below Singer's mathematical threshold for regenerative ability. We now believe that this defect is made up by the stress electrogenic property residing in the bone matrix itself and that the two systems, neural and bone, complement each other to produce the necessary electric threshold for cell stimulation. It has been possible to postulate complete closed-loop, negative feedback control systems based upon this concept for both Wolff's law and fracture healing.

## Promising Clinical Experiments

Within the past few years, initial clinical experimentation has begun in a number of laboratories. While techniques vary and new ones are still being explored, the initial results appear more than promising. Patients, so far, have been limited to those with recalcitrant nonunions of long bone fractures. The success rate has been in excess of 50%, a very good result in view of the nature of the conditions treated.

We believe that the electric factors delivered simulate the control system signals of the initial fracture, which, in the natural course of events, would have gradually declined over a period of a few months postfracture. Each subsequent surgical intervention (ie, bonegrafting, plating, etc) would simulate the initial trauma, but not as effectively and with a shorter time course.

The advantages of the direct electric treatments are obvious, in that they can be controlled to simulate exactly the natural control system and they involve much less operative intervention. One can reasonably expect that with improvements in technique, the success rate in nonunions will be improved over its present value.

## Possible Applications

Further clinical experimentation will be necessary to delineate in detail the future clinical applications. At this writing, in addition to its use in nonunions, the technique would appear to be most immediately applicable to the repair of simple cartilaginous defects. More remote possibilities lie in the areas of: regeneration of portions of joints and, ultimately, complete joint structures; certain bone diseases characterized by growth defects; and corrections of deformities resulting from unequal bone growth. Since malignant growths can be thought of as processes resulting from loss of effective growth control brought on by a variety of causes, the possibility appears tenable that, as such, they might be amenable to electric treatment restoring such effective control. This possibility is being actively explored and, while clinical experimentation has not yet occurred, animal experiments have been encouraging.

This review has emphasized the orthopaedic aspects of these developing concepts. It should be noted that it now appears that what we have all been working with has been a primitive data transmission and control system which provides the substratum for neural activity and regulates many fundamental biologic processes. The future clinical applications in many areas seem to hold much promise.

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