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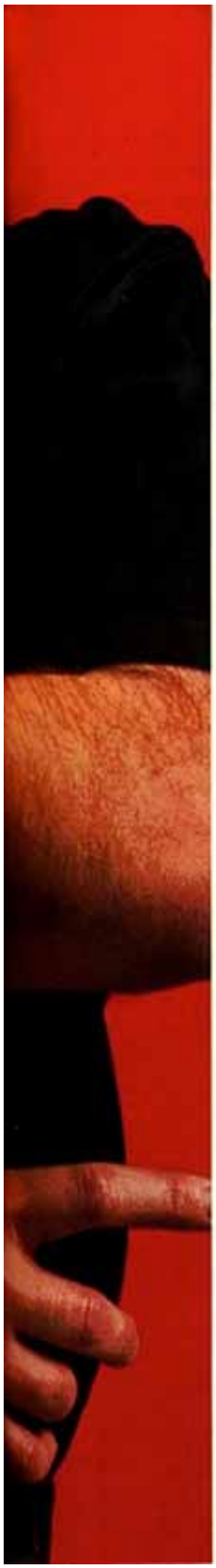


Boosting Our Healing Potential

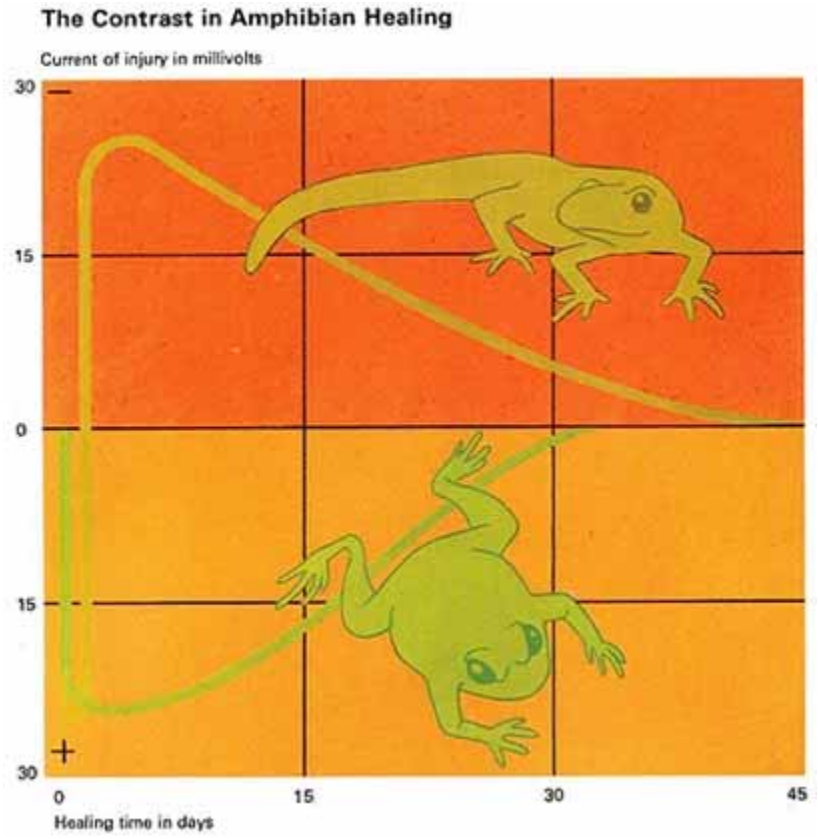
By Robert O. Becker

The discovery of a basic electrical control system in mammals may lead to more efficient injury repair and eventually to regeneration of limbs and organs

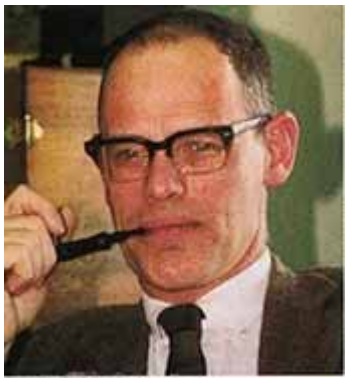
A 45-year-old man came to the Veterans Administration Hospital in Syracuse, N.Y., in February, 1973, with a fractured right ankle. Broken more than two years earlier, the ankle had failed to mend, even after two operations. X rays showed that the bone on both sides of the break had deteriorated. A mild diabetic condition apparently was interfering with the patient's ability to heal. Normally, we would have had to amputate his leg. But this man was lucky.

As an orthopedic surgeon at the Veterans Hospital, I had been investigating a system in animals that seemed to govern healing by electrical control. After 16 years of research on animals, my colleagues and I were ready to apply what we had learned to a human being. We inserted a single silver wire electrode into the patient's ankle. A battery-powered device delivered a constant, tiny electrical current, from 300 to 400 nanoamperes (billionths of an ampere) at 0.2 to 0.8 volt. After two months, we removed the electrode. X rays showed that the bone had begun to heal. After another month, the patient could walk without pain, and X rays showed that the fracture had healed completely. Four months after the start of treatment, we removed a piece of the anklebone and found it to be normal.

The ability of living organisms to heal themselves is one of their most important and basic characteristics. Without it, life could not



The current of injury after amputation of a limb differs markedly in the frog, which heals by scarring, and the salamander, which is able to regenerate the missing limb.



The author:
Dr. Robert O. Becker, an orthopedic surgeon and medical researcher at the VA Hospital in Syracuse, N.Y., has studied the DC control system since 1958.

have evolved. The surgeon relies on this capability, over which he has essentially no control, when he repairs an injury or sutures an incision. But much remains unknown about this self-repair process. What starts healing? What tells it when to stop? Can it be stimulated artificially?

I became interested in these problems in the late 1950s when I found that many of my patients had broken bones that failed to heal properly. In some cases, where the ends of the fractured bones did not touch, the ends had healed over without rejoining. Normal treatment in such cases includes an operation in which we freshen, or scrape; the bone ends. Then we insert bone grafts and perhaps metal pins to hold the bone ends together. However, the procedure does not always work. In addition, several disorders, including certain types of diabetes, interfere with the healing process.

When I started my research in 1957, we knew that healing, like all other biological processes, is a function of the cells. In some way, injury immediately triggers the cells' healing activity, which gradually turns off as healing is completed. Some type of feedback system seems to constantly measure the damaged tissue remaining and adjusts cell activity to produce the exact amount of healing needed.

There are three types of healing, determined by how the cells react to injury. The simplest type is scarring, in which the cells produce scar

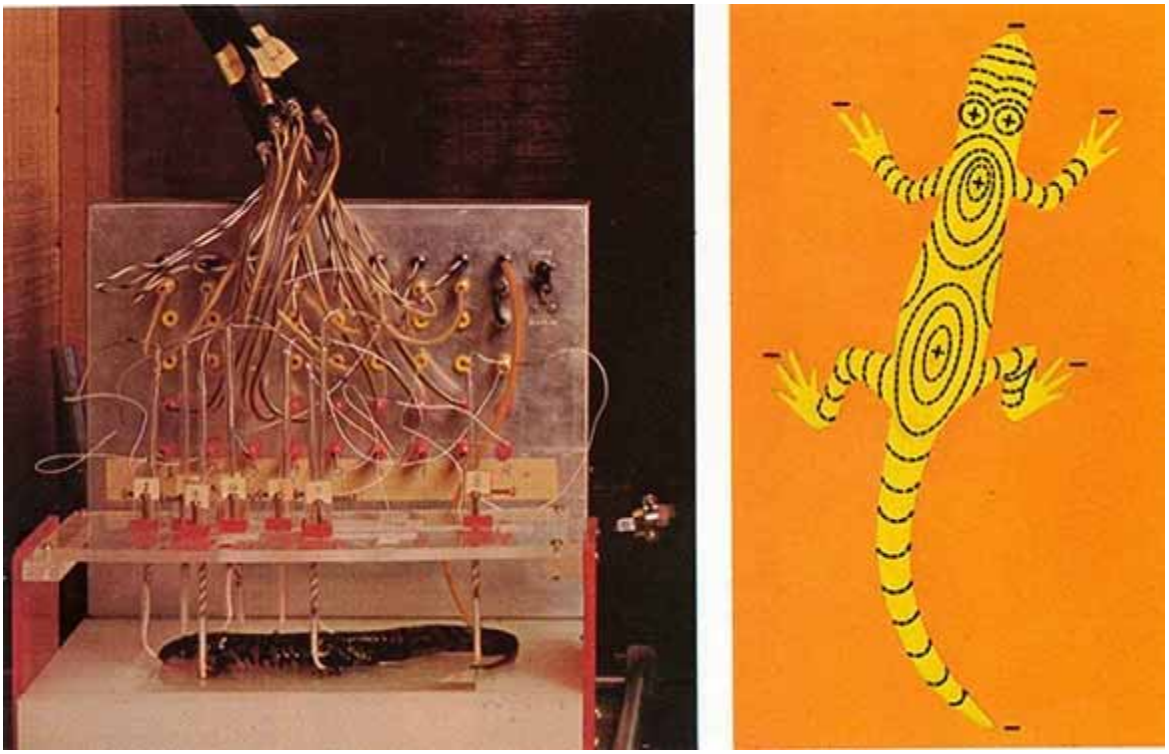
tissue that binds together the edges of the injured tissue. In the higher animals, including man, the heart, skeletal muscle, and nerve tissue, including the brain, heal by scarring.

A second healing process is tissue replacement, in which the cells of some tissues produce more of their own kind to replace missing portions. In man, this process heals skin and parts of the gastrointestinal tract. These tissues are made up of cells that normally "wear out" rapidly and continuously replace themselves throughout life. But there appears to be a limit to the amount of replacement healing possible. Beyond that point, scarring takes over.

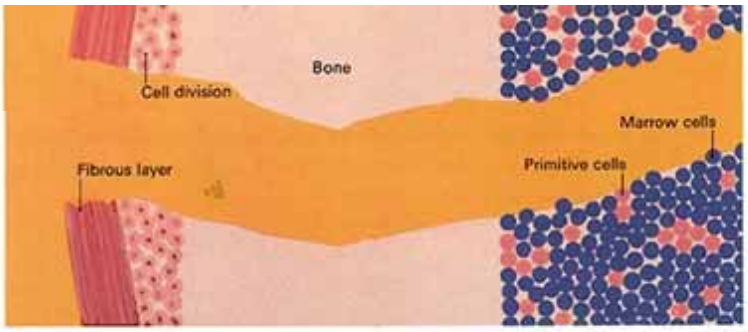
The best and most complex healing process is regeneration. In this process, cells revert to a primitive, unspecialized form when triggered by an injury. These cells concentrate at the site of injury, then respecialize into the different types of cells needed for complete healing. This process can completely restore a single tissue or a complex, multi- tissue portion of the body.

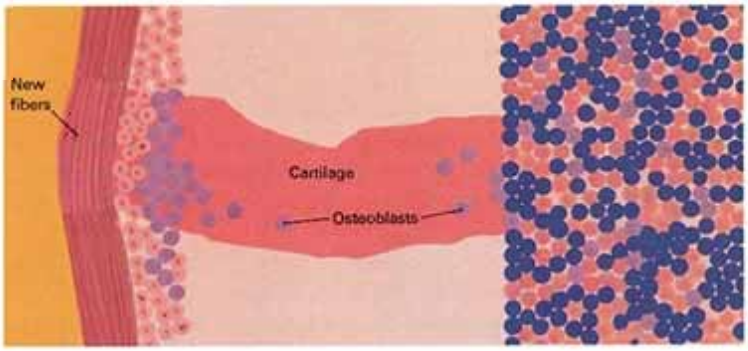
Apparently, the control system that regulates healing becomes less efficient as animals proceed up the evolutionary scale. The most specialized animal with the greatest capability of regeneration is the salamander. It has the same general anatomy as man, yet it can completely regenerate a leg that has been amputated. In man, only bone heals by regeneration. Obviously, it would be beneficial if human beings could regenerate other damaged tissues.

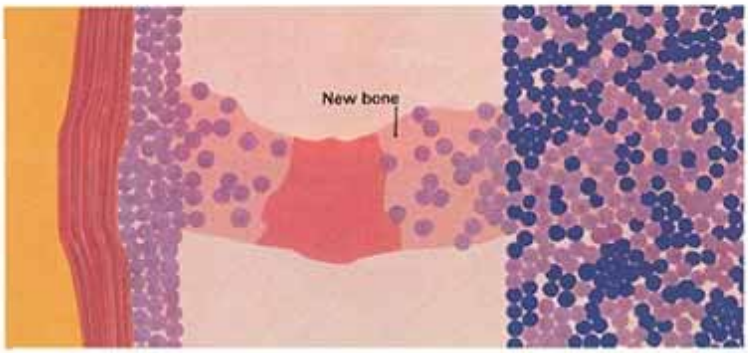
Measuring a DC Field
Electrodes connected to a large salamander, *left*, measure the electrical potentials at several sites to plot its DC field, *below*.



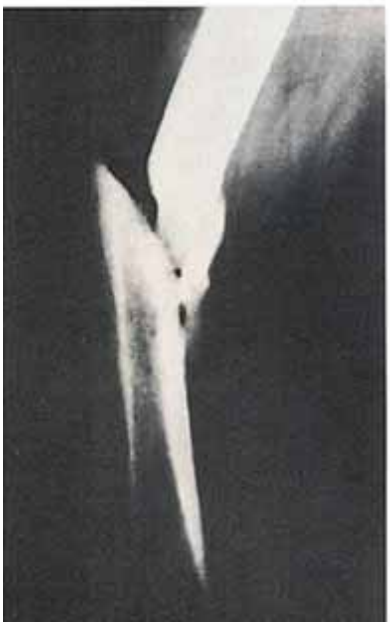
How Fractures Heal
A fracture triggers electrical changes that cause bone membrane cells to divide and produce osteoblasts (bone-forming cells), (left). Marrow cells become primitive cells that also produce osteoblasts, (right).

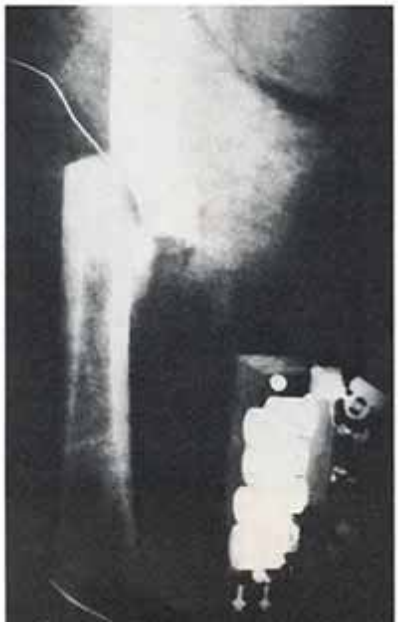


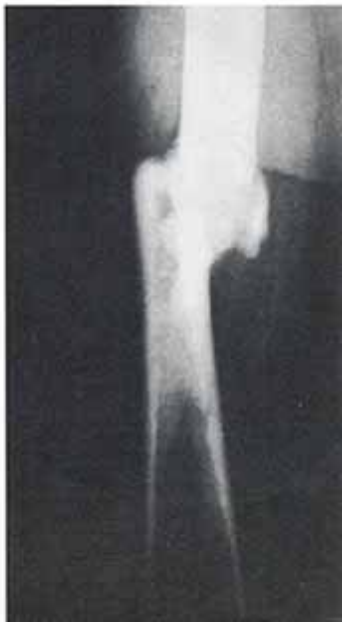




After X rays showed an unhealed thigh fracture in a 22-year-old man, *left*, a battery unit taped to his skin sent a steady current of about 300 nanoamperes to an electrode implanted at the site of the break, *center*. The thigh then began to heal, *right*.







In 1945, S. Meryl Rose, now professor of anatomy at Tulane University College of Medicine in New Orleans, produced the first partial limb regeneration in the adult frog, an animal not normally capable of regeneration. Rose amputated frog forelegs between the elbow and wrist. He then bathed each amputation stump in a strong salt solution every day to retard the scarring and skin regrowth that would nor-mally occur. As a result, about half of each amputated limb, including new bone and muscle tissue, regrew. In some instances, a single digit grew at the end of the limb.

Lev Vladimirovich Polezhaev, a Russian scientist now at the Institute of Developmental Biology, Academy of Sciences, in Moscow, obtained similar results in 1946 by repeatedly puncturing the amputation stumps with a needle. Polezhaev's experiments indicated that Rose's daily salt bathing had produced regeneration by stimulating the cells, rather than by preventing the scar from growing. In the 1950s, Marcus Singer, now professor of anatomy at Case Western Reserve University in Cleveland, produced the same amount of limb regeneration in frog forelegs by transplanting additional nerves from the hind legs into the stumps. His experiments indicated that regeneration would occur if at least 30 per cent of the tissue at the amputation site consisted of nerve.

At this point, we knew that both the amount of injury and the amount of nerve tissue were somehow related to regeneration. But we did not know how they acted. Then, in 1958, a little-known Russian scientist, A. V. Zhirmunskii, began investigating an electrical phenomenon. Measurements on the unbroken skin of any organism show a slight difference in electrical potential, or voltage, between any two points. When an injury occurs, the potential difference between the site of the injury and the surrounding undamaged tissue changes sharply. This is called the current of injury. Scientists have been aware of it since the late 1700s, but modern biologists tend to dismiss it as a simple by-product of the injured cell membranes. However, it was known that the magnitude of the current of injury was proportional to the amount of injury. Zhirmunskii showed that the current of injury also was related to the amount of nerve tissue in the injured area.

When I considered all this, it occurred to me that the current of injury might trigger regeneration. But probably the necessary amount was furnished only when a certain proportion of nerve tissue was present. To explore this possibility, my colleagues and I began studies on salamanders and frogs in 1957. Although these two amphibians are closely related, only the salamander can regenerate its limbs. We amputated a foreleg between the elbow and wrist in each of a group of frogs and a group of salamanders. Then we measured the current of injury with a micro-voltmeter daily until healing-skin regrowth and scarring in the frog, regeneration of the forearm and hand in the salamander-was complete. We reported our results in 1960. The first day, the currents of injury were the same in both animals. But then the

salamanders showed a marked electrical difference compared with the frogs. Both animals initially generated a positive voltage of about 20 millivolts (thousandths of a volt). This gradually declined to zero in the frog. In the salamander, between the third and fifth days, the voltage switched to a negative polarity and then gradually declined, reaching zero when regeneration was complete.

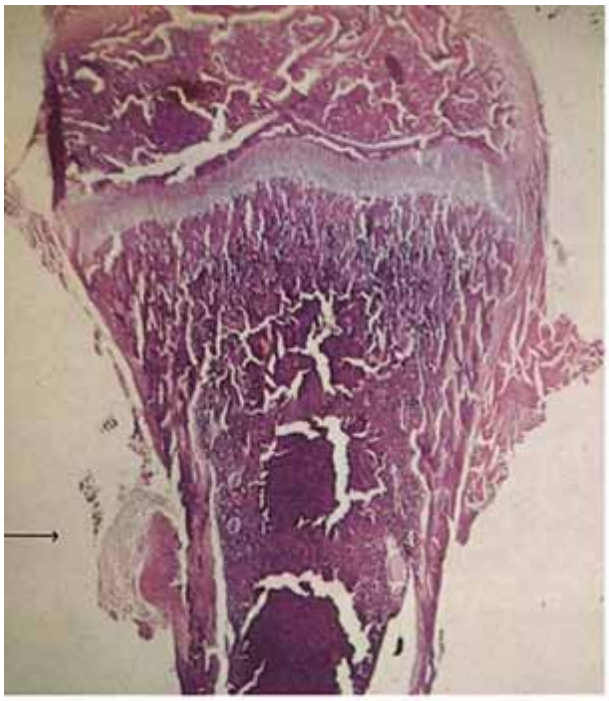
Next, we began searching for the source of the current of injury. Most scientists think that it is generated when damaged cells allow electrons to "leak" through the cell membranes. We knew, however, that this was not the complete explanation. We had found measurable currents of injury in both frogs and salamanders many days after injury. Damaged cells either die or repair themselves within a day or two; they could not produce such long-lasting electrical factors.

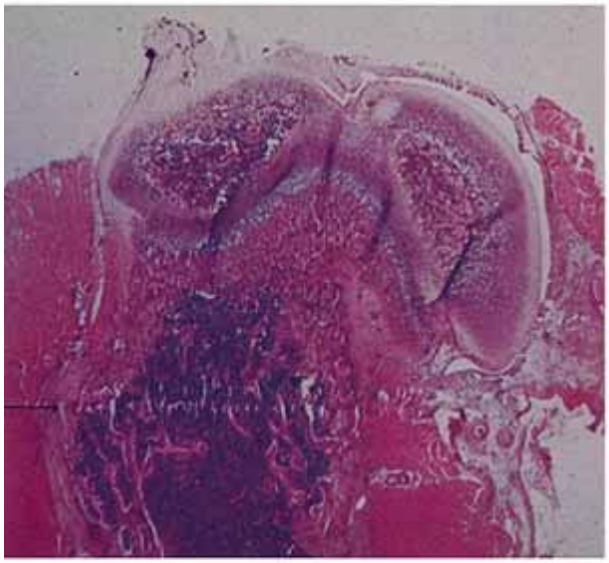
We began our search for the source of the current of injury by following up Zhirmunskii's theory of a connection with the nervous system. We knew that the nerves transmit the information that allows us to see, feel, hear, smell, and taste by means of nerve impulses. But there were indications that there might be other ways of transmitting more basic data, such as pain, or the control of healing and growth. The nerve impulse system is a high-speed, sophisticated communications system that transmits very complex data. The first primitive living organisms could not have had such a system, yet they must have had some means of communicating information within themselves—of sensing injury and repairing it, for example.

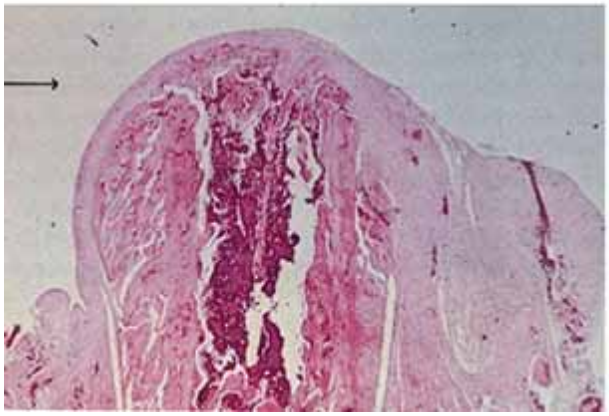
We suspected that the current of injury might be related to this more basic transmission system. We began our investigations in 1960 by measuring the electrical potentials between many different points on the skin of human beings and many other animals. We found that the potentials are organized into an electrical field, represented by lines of force, that roughly parallels the pattern of the nervous system. Changes in the field must permit information to be transmitted to and from the living cells throughout the body. An injury produces a local disturbance in the field pattern, stimulating the cells to regrow and heal the injury. We thus concluded that the field was the primitive data transmission system that took care of more basic functions than the nerve impulse system.

We also found that the field appeared to be directly associated with some element of the nervous system that generated and distributed the potentials. Electrical potentials in a conducting medium such as the nerve cell implies there also is a steady direct current (DC) flow.

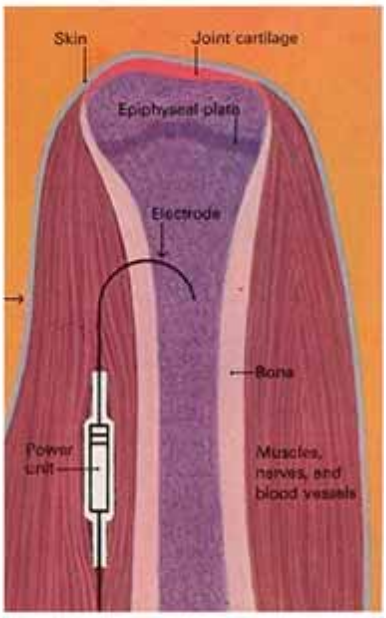
To discover how the nerves generated and transmitted the current, we isolated living nerves within several animals, leaving the nerves still connected to the animals. We then studied the effects that anesthesia, injury, temperature changes, and cutting the nerve had on the potentials. Our results, reported in 1963, seemed to indicate that the nerves not only transmitted impulses, but also that electrons actually flowed within some element of the nerves. Furthermore, the way they flowed





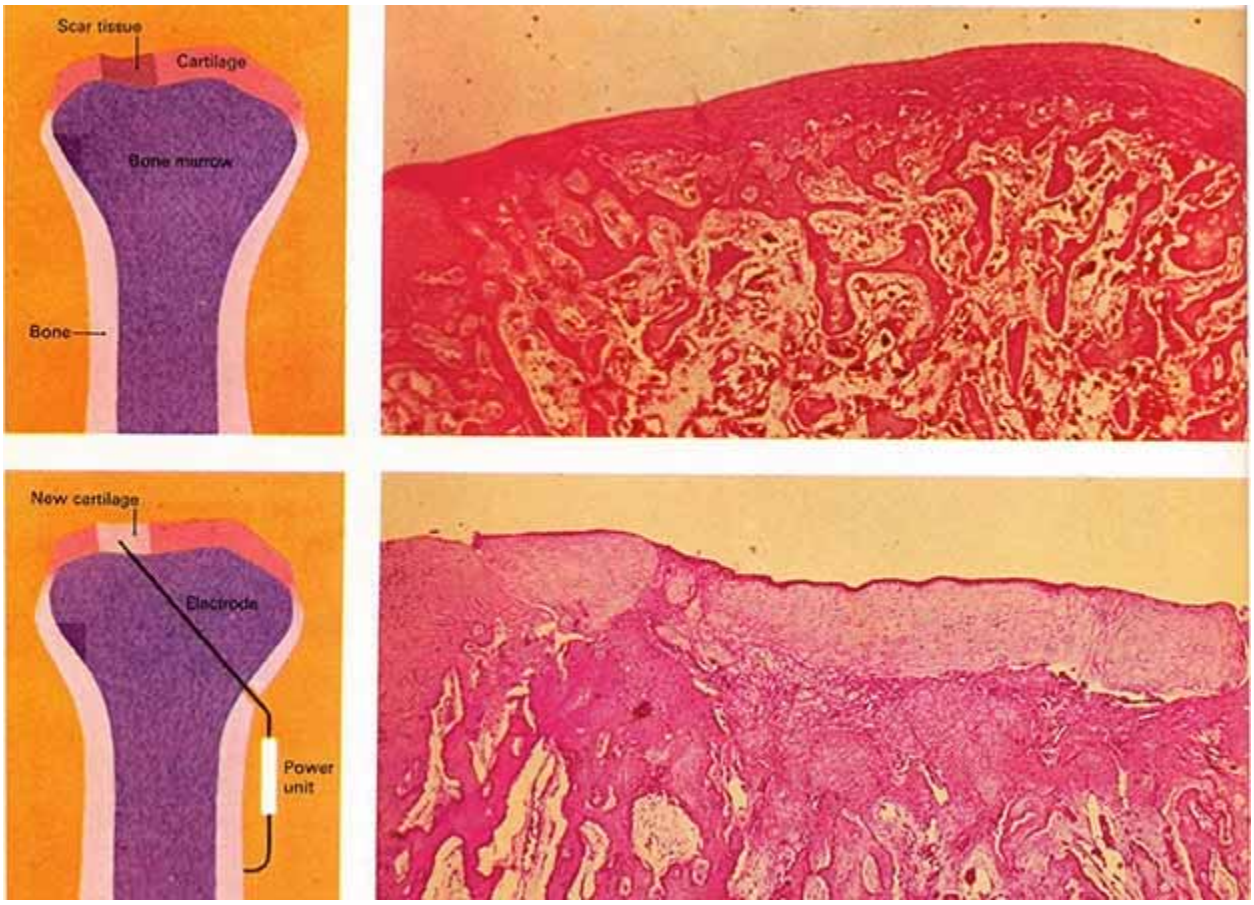


Some Regrowth of a Rat's Leg



A rat foreleg, *top left*, was amputated between the shoulder and elbow joint (arrow). A small device, *above*, in the stump supplied a tiny electrical current that produced partial regeneration of the leg, including bone, muscle, nerves, blood vessels, and joint cartilage, *center*. Without treatment, an amputated limb will simply scar over, *bottom left*.

Regenerating a Rabbit's Cartilage



Damaged joint cartilage in a rabbit normally heals with scar tissue, *top*. With the help of an electric current, the cartilage regenerates almost wholly, *above*.

implied that a very ordered crystallinelike arrangement of atoms existed somewhere in the nerve tissue. But experiments aimed at finding these atoms were very difficult because the nerve is composed mostly of water. As a result, we could not identify the portion of the nerve that carried the electron flow.

So we turned our attention to bone. Bone can regenerate even though it has far less nerve tissue than is needed for this process. This indicates that bone might contain its own electronic healing control system to make up for t he deficient nerve supply. If we could discover how this system works, we would probably get important clues to how the overall healing control system operates. In addition, bone is easier to study than nerves. It is mostly solid, and has a well-organized structure that has been studied in submicroscopic detail.

We began by studying a bone-growth process that, although simpler than the growth involved in healing, appears to be equally well controlled. This is the growth of bone in response to mechanical stress. Bone constantly alters itself to produce the shape that best resists stress.

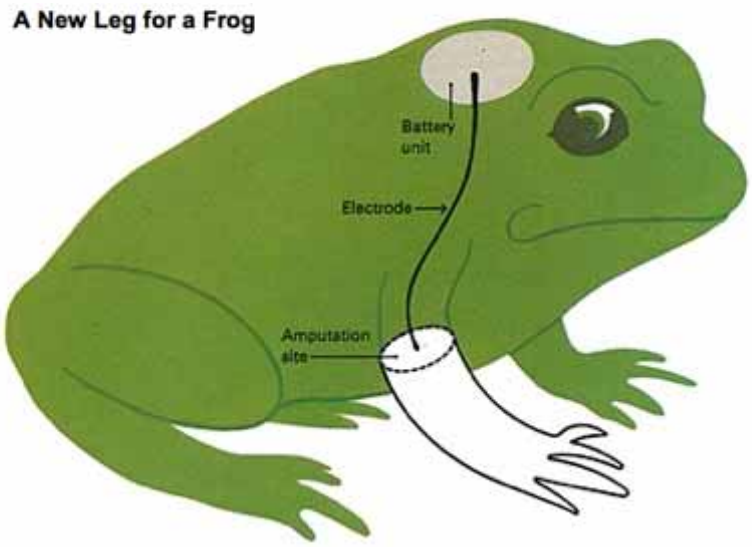
This is as if a bridge could sense the loads applied to it by traffic, wind, and tides, and constantly adjust its structure and strength to accommodate them. For example, when a bone is bent, one side is compressed ,and the other side is stretched. The bone grows on its compressed side and dissolves on its stretched side. We wondered whether bone responds to such mechanical stresses by generating electrical potentials proportional to the stress and whether these potentials then stimulate bone cell growth.

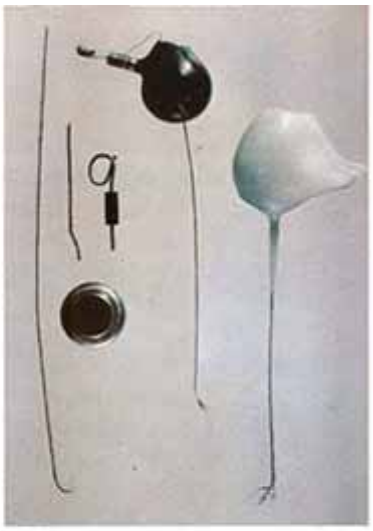
To find out, we removed bones from frogs and other animals and placed them in insulated clamping devices that left one end free. We attached electrodes at various places along the bone shaft and then recorded the electrical potentials that were gene rated as we bent each bone. We found that the compressed side becomes electrically negative and the stretched side becomes positive. If these differences in electrical potential regulate bone growth under stress, we reasoned that inserting electrodes into the bone and running the appropriate current through them should cause bone to grow at the negative electrode and to dissolve at the positive electrode.

In 1964, we tested this concept on adult dogs in conjunction with C. Andrew L. Bassett, research professor in the Department of Orthopedic Surgery at Columbia University College of Physicians and Surgeons in New York City. Into the bone of one hind leg, we inserted a small battery-powered unit with two platinum electrodes penetrating the bone, one centimeter (0.4 inch) apart. As a control, we inserted a similar unit, without the battery, into another leg. After two weeks, microscopic examination of the leg with the battery unit showed considerable new bone growth around the negative electrode. There was no bone growth around the positive electrode, although some would have been expected simply to repair the injury caused by the electrode insertion. This indicated that the positive electrode had prevented new growth, or else had dissolved any new growth as fast as it occurred. In the control leg, without the battery, bone growth was identical around both electrodes. We tested currents ranging from l to 10 microamperes (millionths of an ampere) and found that currents between 2 and 5 microamperes produced the most growth.

Next, we studied the regenerative process of bone healing by applying electrodes to frogs' broken leg bones to measure the electrical potentials. Experiments with several hundred animals revealed that the potentials lasted much longer than those found with simple bending stress and produced a more complex electrical field centered at the break. We also found that the difference in the potentials in the broken leg promptly dropped to almost zero when we cut the nerves to the site of the break. This indicated that the electrical field depended partly on the nerves.

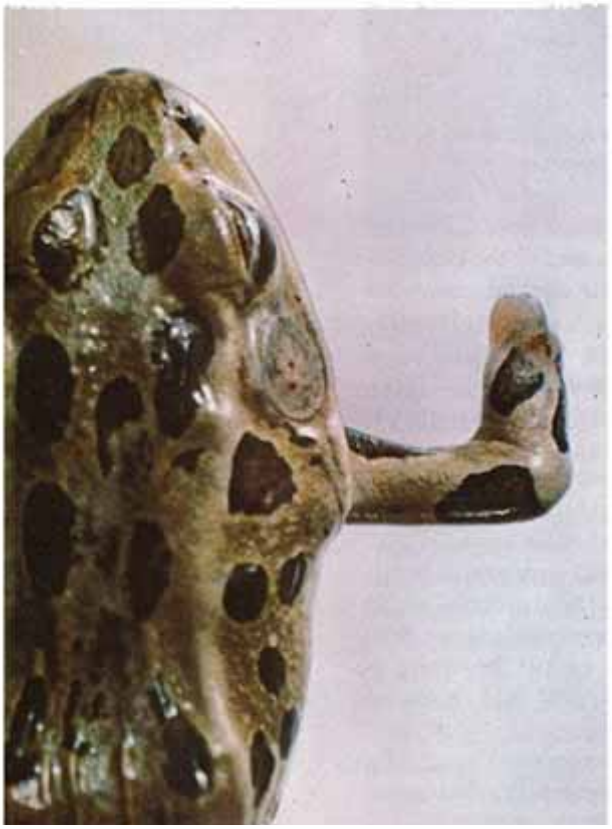
We viewed the healing process through a microscope and noted the cell changes in the blood clot surrounding the fractures that led to the formation of a mass of primitive cells which then became new bone.





The implanted healing device is embedded in silicon rubber to prevent rejection.

An amputated frog leg was completely regenerated for the first time in 1973. A battery unit was implanted in the frog's back and a lead wire was run down to an electrode at the amputation site, *above*. The stump, *below left*, grew into a new leg and foot in about one year, *below right*.



Next, we attempted to produce the same changes in normal cells. We placed blood cells from the frog in plastic chambers and exposed them to the same electrical field we had found around the broken bone. The cells responded exactly as had those at the site of the break. This proved that the electrical field found at the fracture site controlled the cellular changes that led to regeneration. Most important, we were able to determine very precise ranges of voltage and current that most effectively produce the desired changes. For cells in a chamber 1 centimeter in diameter, we achieved the best results with currents of about 0.5 nanoampere. Currents below 0.1 nanoampere and above 0.9 nanoampere were much less effective in producing the changes that lead to regeneration.

By 1970, we could trace in detail a control system for the bone-healing process. A fracture produces local changes in the DC field in two ways. Like all injuries, it stimulates the neural system, which produces a DC electrical signal at the fracture site. In addition, the bone produces its own electrical signal in response to stress. The combined changes stimulate two types of cells. The cells of the membrane covering the surface of the bone begin dividing rapidly to produce osteogenic, or bone-forming, cells. At the same time, the red blood cells of the bone marrow revert to primitive cells, which then respecialize into osteogenic cells. As these cells produce new bone and the fracture heals, the electrical field gradually returns to normal.

Learning what we have about the bone healing control system has had two important results. We found that the control system can be reactivated in human patients whose fractures fail to heal, by supplying the proper currents at the appropriate site. This technique is now being evaluated at several medical research centers, both in the United States and other countries.

Also, our knowledge of the control system for healing broken bones suggested a control system that regulates regeneration in other tissues. According to our concept, organisms lose regenerative ability as they increase in complexity because more and more of their nerve tissue is concentrated in the brain, leaving less available for the rest of the body. With less nerve tissue, the body cannot provide the voltages needed to trigger regeneration. We still cannot explain why the adult human brain heals by scarring instead of regeneration, although some studies indicate that infants can regenerate brain tissue to some extent.

We reasoned that if we could induce the missing voltages in the stump of an animal's severed limb, its cells might return to a primitive type and respecialize into all the cell types necessary to regrow the missing part. The first attempt at this had come in 1967, when Stephen Smith, a graduate student working with Rose, produced partial regeneration of an amputated leg in the frog. He duplicated the salamander's current of injury in the frog by implanting in its leg a short piece of silver wire soldered to a short piece of platinum wire with the negative end in the stump. The solder joint and adjacent parts of both

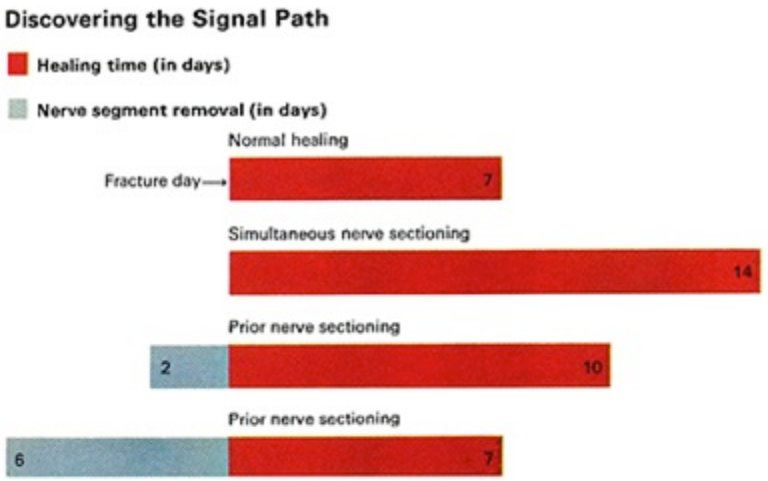
wires were covered with insulation. Such a device, when placed in any conducting solution, such as tissue fluid, generates a small amount of electricity. In effect, Smith's device was a crude battery that generated 300 nanoamperes at 0.1 millivolt. It produced the same amount of regeneration in a frog's amputated leg as did the experiments of Rose, Polezhaev, and Singer.

By 1972, we were ready to try a similar experiment on mammals. We amputated one foreleg between the shoulder and the elbow in each of a group of laboratory rats. We modified the bimetallic device Smith had used in earlier experiments by inserting an electrical resistor in place of the solder joint. We inserted one electrode into the marrow cavity of the bone at the amputated end, and sewed the other end in the shoulder muscle. By varying the size of the resistor, we were able to test the rate of healing using devices with high, medium, and low currents. As a control, we studied the rate of healing in animals that were not fitted with devices.

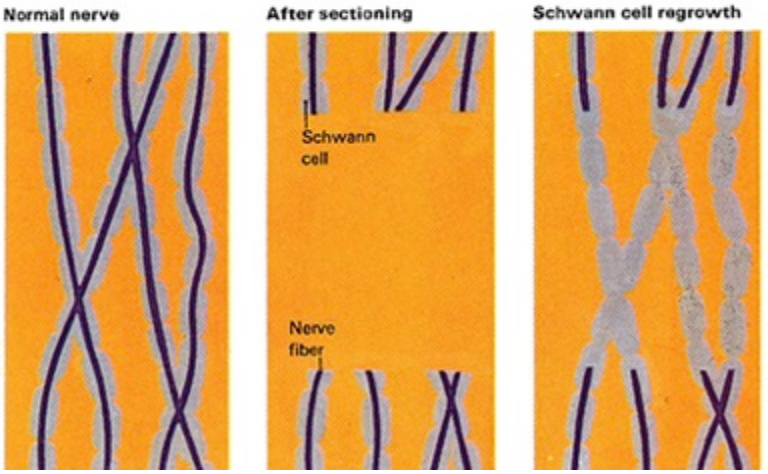
In the controls, as expected, the bone grew closed at the end and the amputation stump scarred over. The animals with low-current devices (0.1 nanoampe re at 350 millivolts) had a small amount of regeneration. The high-current devices (15 nanoamperes at an immeasurably low voltage) seemed to destroy, rather than regenerate, tissue. Animals with medium-current devices (5 nanoamperes at 75 millivolts) showed varying degrees of regeneration. The best results occurred in one rat with a device that produced 8 nanoamperes at 100 millivolts with a 10 megohm (million ohms) resistor. This regenerated the missing portion of the upper limb down to the elbow joint, including regrowth of muscle, nerve, bone, and blood vessels.

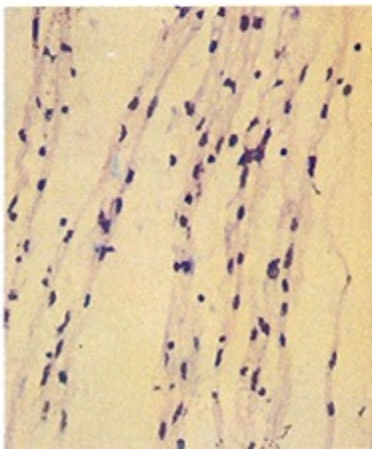
While we had not restored a complete limb in the rat, we had succeeded in growing normally organized complex structures composed of many different types of cells and tissues in a mammal, the first step toward similar work in humans. And, we had achieved such growth through an electrical stimulus. Further evidence that regeneration could be electrically induced came in late 1973 when Smith, now associate professor of anatomy at the University of Kentucky in Lexington, reported that he had regenerated the entire foreleg in a frog, using implanted battery-operated devices.

In 1973, we used rabbits to investigate a regenerative process that could affect the treatment of arthritis. All types of arthritis occur because injured cartilage heals only by scarring. Scar tissue cannot withstand much pressure and the pain of arthritis develops rapidly. Because cartilage is a single tissue, we reasoned that stimulating it to regenerate would be easier than working with an entire multitissue limb. We removed a piece of cartilage from the knee joint of each rabbit, then inserted a medium-current, bimetallic device. After three weeks, all of the animals with devices had regenerated some cartilage and a few had regenerated almost all of it. With Bruce Baker, assistant professor of orthopedics at Upstate Medical Center in Syracuse, we



The time to heal a broken leg in a mouse is doubled if a segment of nerve is removed at the same time the leg is broken. But the leg heals in normal time if the nerve segment is removed six days before the break. Microscopic examination shows that the Schwann cell sheath bridges the gap and apparently carries the healing signal.





are testing battery-operated devices to try to get complete healing in all cases, and to search for side effects.

But there was still a missing link. We had not identified the part of the nerve that transmits the control signal for healing.

We knew that the nerves' role in fracture healing was rather mysterious. For example, the patient who is paralyzed by an injury to the spinal cord can neither feel nor control muscle movement below the point of his spinal cord injury. But broken bones in this part of his body heal about twice as fast as normal. This is because the nerves to this part of the body are still intact and functioning, but the spinal injury has separated them from the regulating influence of the brain, which normally keeps healing under stricter control. However, in patients with damage to the peripheral nerves (those serving the extremities), broken bones heal very slowly or not at all.

We used laboratory mice to explore the subtle relationship between nerves and the healing of broken bones. First, we broke a small bone in

Electrical Needlepoint

Scientists have not yet been able to explain how acupuncture works. Practitioners of this ancient Chinese technique relieve pain and treat disease by inserting long, fine needles into the body at various points and rapidly twirling them. While the value of acupuncture in treating disease is hotly debated, its effectiveness as an analgesic, or pain reliever, for some people is generally accepted.

According to legend, acupuncture originated more than 3,600 years ago when Chinese Emperor Shih Huang-ti noticed that the soldiers who received arrow wounds in battle sometimes had ailments cured in other parts of the body. The first published reports appeared about 500 B.C. In succeeding years, Chinese doctors worked out an elaborate theory to explain acupuncture based on the flow of energy along 12 pathways, or meridians, in the body. They believed that an imbalance in the flow caused disease and pain. But needles inserted at specific points along the meridians would change the flow, correct the imbalance, and restore health. Acupuncture charts show at least 350 points where needles can be inserted into the body.

Instead of twirling the needles, acupuncture practitioners sometimes apply either continuous or pulsed direct current (DC) electricity to the needles, as another form of stimulation (see SHUTTING THE GATE ON PAIN). There are also reports that the acupuncture points may be precisely located by measuring the skin's electrical resistance. The points appear to have much lower resistance than the surrounding skin. These electrical effects cannot be explained on the basis of the known functions of the nervous system, but they seem to fit the concept of the DC communications system that my colleagues and I have developed.

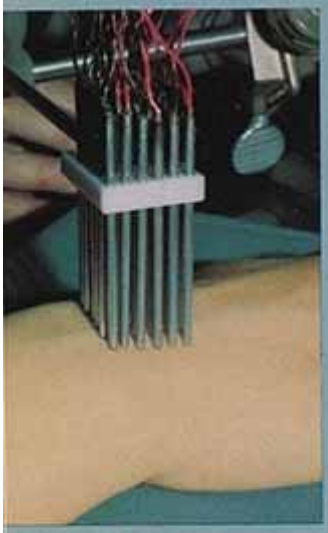
In fact, the existence of the acupuncture points can be predicted by any electrical engineer who understands our studies. An engineer designing a system to transmit direct current must allow for factors called cable constants. Examples of cable constants are resistance and capacitance, which cause a current to lose strength progressively as it travels along the wire. Engineers overcome this loss by inserting amplifiers, or boosters, at strategic points along the transmission line, so that the original signal is delivered at full strength at its destination.

If our theory of a DC control system is correct, such amplifiers must exist along the course of the Schwann cell transmission lines in order to carry the control signal for healing. The sites of these amplifiers would also be sources of DC. To find the sites, we measured electrical resistance at various points on the skin because it is much easier to measure resistance than to find evidence of DC emission. The sites appear as points of diminished resistance. We measured resistance at 22 listed acupuncture points on the forearm and found significantly decreased resistance at 11.

We are now looking for evidence of DC emission from those points in the forearm that register decreased resistance. We use a device called the high resistance electrometer to measure the electrical potential. So far, we have found DC current emitted at enough points to indicate that we are probably correct in describing these "low resistance" points as DC sources.

Next, we plan to search for evidence that the DC system can transmit messages in two directions within the body. We plan first to measure the potentials at, say, six points along an acupuncture meridian. Then we will attach electrodes to the five points nearest the body and insert a needle into the sixth, or farthest, point. If our theory is correct, we should see a change in potential move progressively from point to point. We can measure the change and also how much time it takes to move. This would be evidence that a message is being transmitted and would firmly substantiate our thesis of a DC control system for healing.

It would also indicate that inserting needles into the body may not be the most efficient way to administer acupuncture analgesia. If the system is as we envision it, applying carefully measured electrical current alone may give the best results. Small battery-operated devices could deliver the necessary electrical pulses through skin surface electrodes to provide safe, easy, and effective analgesia. [R.O.B.]



A multielectrode probe measures the electrical field surrounding an acupuncture point on the human forearm. Emissions from some points seem to support the theory of the DC communications system.

the hind leg, leaving the nerves intact, and examined the break microscopically each day until it healed. This showed us how the cells changed and how long it took to heal the break.

Then, we broke the same bone in another group of mice and also removed a quarter-inch segment of the main nerve to the hind leg. We wanted to produce a major defect that would interfere with healing as peripheral nerve damage does in human beings. But all the bones did heal, although healing took twice as long as normal.

Next, since we were trying to produce a condition that would prevent the bones from knitting, we removed segments of the nerve two and three days before we broke the bones. We thought that this would produce partial degeneration in the part of the nerve that we had separated from the rest of the nervous system. But the result was just the opposite of what we had hoped for. The fractures healed faster than when we broke the bone and cut the nerve at the same time, though not quite as fast as normal.

Still hoping to prevent the bones from joining, we removed the nerve segments five and six days before breaking the leg bone. To our surprise, the mice responded as if the nerve had not been cut at all. The bones healed in a normal amount of time.

It was highly unlikely that the nerve itself had regrown, and microscopic examination of the interrupted nerves showed that this was the case. Obviously, the nerve was not the tissue that transmitted the healing control signal after all. However, we discovered that another thin tissue had bridged the gap in the nerve. In late 1973, we identified this tissue as the Schwann cell sheath, which surrounds each peripheral nerve. We now believe that the Schwann cell sheaths transmit the healing signal, at least in the limbs.

More important, our experiments provided a clue to the source of the entire primitive data transmission system. The Schwann cells are part of a group of cells known as the perineural cells. These are derived from the same tissue that forms the nerve, and they form a complete network that pervades the entire central nervous system, extending from the Schwann cells, which surround even the smallest peripheral nerve, to the glial cells, which form a complex mass in which the brain cells are imbedded. It was known that the glial cells have different electrical properties than the nerve cells, such as slow waves and steady potentials, yet their function was largely unknown. Our work indicates that all the perineural cells link together to form the primitive data transmission system we sought.

As we learn more about how the healing system works, we will begin to use it medically—from controlling pain to regenerating complex tissues. We have already helped to repair broken bones that refused to mend by themselves. Soon we may be restoring the damaged joint cartilage that leads to arthritis. And I believe that, in time, we can induce total regeneration in man, not only in his limbs, but also in his heart and other vital organs.