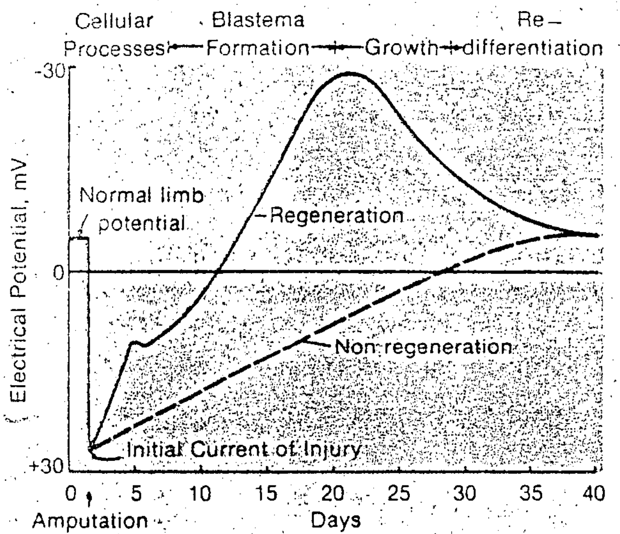

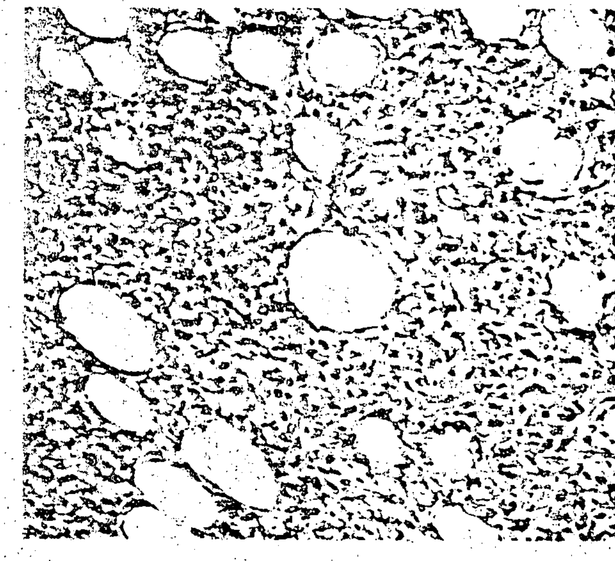

The diagram at left shows the difference in the amounts of current found at an amputation site in animals that are capable of regeneration (solid line) and animals that cannot regenerate lost limbs (broken line). At right, a microphotograph of dedifferentiated amphibian erythrocyte during the passage of electrical current.

Electric current sparks mammalian tissue regeneration

One of the most fascinating medical mysteries is why an amphibian such as the salamander can regenerate missing parts, while a human in similar straits must simply do without.

For the past 12 years, this mystery has occupied the concentrated attention of Robert O. Becker, MD, associate chief of staff for research at the Veterans Administration Hospital in Syracuse, NY.

One theory has it that the ancestors of mammals possessed regenerative ability in the very distant past, but lost it when evolution reached the point where most of the body's electrical activity occurred in the brain.

This theory is, at least in part, subscribed to by Dr. Becker who recently has had satisfying results in getting limb regeneration in rats. Earlier, he worked extensively with frogs—animals that also do not normally regenerate limbs.

"There is a lot of interest in regeneration," Dr. Becker said in an interview with *JAMA* MEDICAL NEWS, "but most of it relates to clinical applications. There isn't much at the basic level, except among the Russians, who have done a lot of important work in the field."

Regeneration is brought about by electrical stimulation of cellular activity. The electrical stimulus causes cells to "dedifferentiate" and leads to the formation of masses of blastocytes. These cells then become redifferentiated into the missing part. A blastema must be formed before regenerative growth can occur.

An important key to the process is strength of the electrical current, which must be exactly right. Get it too low and nothing happens; get it too high and tissue is destroyed—a phenomenon that could some day become clinically useful in slowing down or reversing tumor growth.

For his research, he used one experimental group and three control groups. All the rats had their right forelegs amputated at the junction of

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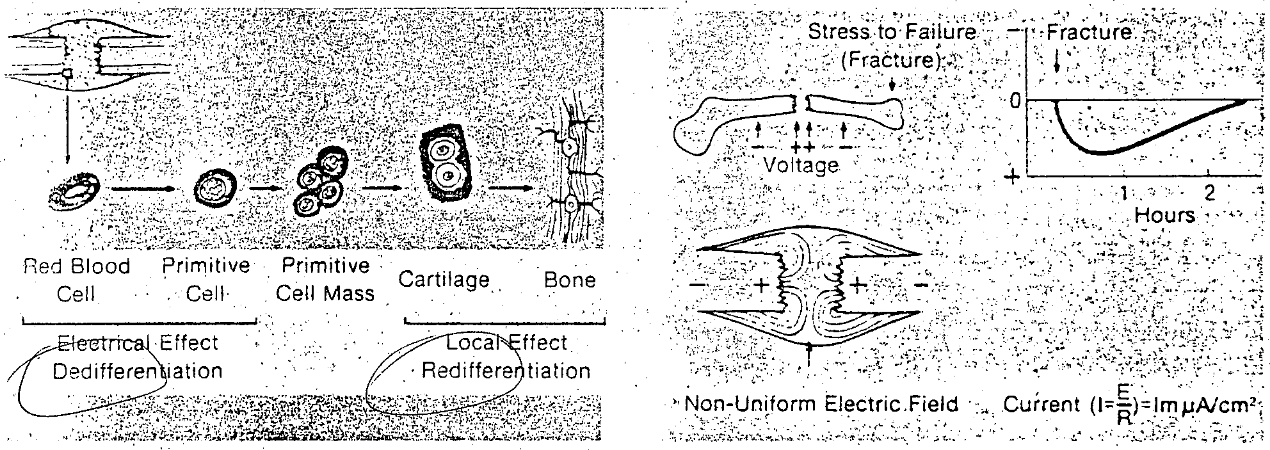

The diagram at left shows the cellular events involved in fracture healing among non-mammalian vertebrates. At right, the electrical field resulting from fracture is basically an opposed dipole that lasts for hours, unlike the signal from simple stress that has a duration of only seconds.

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the middle and lower thirds of the humerus. This was all that was done to rats in control group A, while low current generating devices were implanted in the stumps of group B rats, and high current generating devices in group C rats. A fourth (experimental) group of rats received devices generating what the investigator considered the right amount of current.

The results:

Rats in group A (simple amputation only) had subperiosteal osteogenesis and bridging of the cut surface with new bone and formation of a simple fibrous cap. Rats in group B had more bone growth but no recognizable blastemas. Rats in group C had bone destruction and cyst formation. However, in the fourth group of rats (implanted with devices generating 3 to 6 nanoamperes) there was clear evidence of regeneration, consisting usually of regrowth of the distal humerus complete with two epiphyseal centers.

Although interest in the subject goes back hundreds of years, modern work dates from 1945, when an adult frog was induced to regenerate a limb by repeated trauma. Dr. Becker also worked first with frogs and followed this with human cell studies. Using electrical stimulation, he was able to get two types of human cells (stem cells and lymphocytes) to produce blastocytes, showing that regeneration is theoretically possible.

The only true regenerative growth process remaining in mammals is fracture healing, which involves two cellular processes. First, mitotic activity takes place in the periosteum, and second, dedifferentiation occurs in bone marrow where the blastema is formed.

Lately, it has been found that electrical stimulation by direct current can promote faster healing of broken bones. Dr. Becker does not view this treatment with any marked enthusiasm and explains his position thusly:

"There are few regulations concerning medical devices using electricity, as opposed to the circumstances relating to new drugs. Yet, the effects produced at the cellular level by the injection of extremely small electrical current indicate that we have gained access to biological control systems of a very basic nature. We appear to be about to tamper with the basic stuff of life itself, and I believe that there are several very real dangers inherent in the premature widespread use of these techniques."

Noting that administration of direct current to bone marrow leads to morphologic conditions similar to those associated with a fast-growing osteosarcoma, he expressed concern about the possibility of producing a malignant transformation of cells.

Another reason for caution, according to Dr. Becker, is that applying electric current to the central nervous system could induce behavioral or cognitive disorders that also might not be evident for years.

"The desire for immediate clinical rewards might be such," he continued, "that applications of an extremely important nature might be overlooked. Even worse, there is the possibility that acceptance of this technique as clinically useful might lead to quacks selling ineffective, but costly, 'treatment devices' with this end result: Rejection of the entire concept."

In addition to promoting bone healing, other areas of which electromagnetic energy is being used now include treating inadequate bone growth, promoting rapid healing of skin ulcers and burns,

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- No apparent differences exist between patients who receive anti-lymphocyte globulin (ALG) or anti-thymocyte globulin (ATG) with respect to survival, rejection frequency, rejection score or the total dose of methylprednisolone used in the early postoperative period.
- Reinnervation of the transplanted heart does not occur.

Indeed, it has become clear that "the vascular lesions of chronic allograft rejection" are the most important determinants of long-term survival, said Dr. Griepp. The lesions consist of intimal thickening—made up of fibrocellular tissue—in the large coronary arteries, with and without atheromatous plaques.

The theory is that the presence of humoral antibody or infiltrating mononuclear cells results in proliferative repair and scarring of the intima. Platelet and fibrin microthrombi form on the exposed rough subendothelial surface, thus organizing and thickening the intima. Then, in patients predisposed to coronary atherosclerosis by hyperlipidemia, lipophages, and free lipids accumulate in the intracellular matrix and this leads to further inflammatory intimal thickening.

In an attempt to avoid or minimize these vsacular lesions, the Stanford workers began a prophylactic regimen with their 17th patient. This included maintenance of ideal or lower weight, restriction of dietary saturated fat and cholesterol, and administration of warfarin sodium and dipyridamole, a platelet antagonist. They also began a program to detect coronary artery narrowing: this consisted of bimonthly exercise electrocardiography and annual coronary arteriography.

Preliminary results demonstrate the effectiveness of the regimen. Of the first 16 patients, who were not put on the regimen, 8 survived the early postoperative period. One year after transplantation, 3 of the 8 had postmortem or arteriographic evidence of coronary lesions, and there was no proof that the other 5 did not. Seven of the 8 patients had evidence of coronary lesions at the end of two years.

In the second group of 16 patients (who were placed on the prophylactic regimen) 9 survived the early postoperative period. One year after transplantation, 8 of these 9 were known to be free of coronary lesions. (No evidence was available for the ninth patient.) In this group, three of four patients who underwent transplantation more than two years ago are known to be free of coronary lesions, Dr. Griepp said.

Dr. Shumway, Eugene Dong, Jr., MD, and Edward B. Stinson, MD, collaborated in the study.

Tissue regeneration research advances

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producing sleep or general anesthesia, and as an adjunct to acupuncture.

Dr. Becker would like to see a clearinghouse of information on the subject established before long, "or else we will lose data or miss information on side effects."

He remains confident that the time will come when at least limited regrowth of limbs will be possible for humans. But, prior to that, and shortly, he expects to see important clinical applications in single tissue regeneration. His most recent work has shown it is possible to enhance cartilage regeneration in the joints of mammals. At a much later stage, this could be of great importance to persons with arthritis.

"It comes down to just sorting out all the factors," he said. "We need to look at hormonal response, at the availability of data-carrying channels, and the relationship between the raw amount of nerve and total bulk, in addition to finding the right amount of electrical stimulation."

The information on hormones has special significance. In his earlier work with frogs, he and his co-workers discovered that it took more current to dedifferentiate frog erythrocytes in winter than in summer. This effect was traced to seasonal variations in concentration of prolactin in the tissue.

Dr. Becker has an average of 14 people working with him at any given time in his Syracuse laboratory, and the group now is involved in assaying enhancement of bone growth.

Another significant research project planned for 1973 is clinical testing on whether electrical activity can be used to inhibit cell growth in patients with tumors.

"It stands to reason," he says, "that if we can cause cells to grow, we should also be able to inhibit growth." He will use only patients for whom all other techniques have been exhausted and he does not expect any cures. "We will be assaying results of the appropriate electrical parameters."

He noted that there will be at least four major conferences on regenerative growth this year and concluded by calling for a multidisciplinary approach to both limb regeneration and other medical uses of electromagnetic energy.

"Right now," he remarked, "it's mostly in the hands of a few biologists, but we could achieve fantastic results within four or five years if we get others involved."