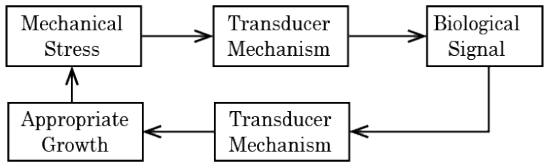
The Control System Governing Bone Growth in Response to Mechanical Stress*

Robert O. Becker, M.D.**

Bone grows in response to applied mechanical stress in such a fashion as to produce an anatomical structure best able to resist the stress. This phenomenon, first described by Wolff in 1892,[1] is of considerable clinical importance, enabling the bone structure of the body to be in a dynamic equilibrium with the changing mechanical stresses imposed by activity. This growth phenomenon is quite different from both epiphyseal growth and fracture healing, in that it is continuously going on, producing rearrangement of structure in response to changing stresses. In its' simplest form, that of the response to bending stress, the concave or compressional side experiences increased growth resulting in the laying down of new osteones along the lines of stress while the convex or tensional side experiences resorbtion of bone elements. This process is amenable to study by standard control system concepts and appeared to offer considerable promise for giving us some insight into growth phenomena in general. Some years ago my colleagues: Dr. C. A. L. Bassett, of Columbia University and C. H. Bachman, of Syracuse University and myself began such a study.

In analyzing this growth process as a "simplest possible" control system; i.e. as a closed loop negative feedback chain, one arrives at the following control system diagram:



Obviously the bone in some fashion senses the stress applied, this implies some mechanism for converting the mechanical energy into a signal which must be proportional to the magnitude of the stress and indicative of the direction of application. The signal must activate a second transducer mechanism that produces bone growth along the lines of stress.

Because of previous work on regenerating growth systems[2] we postulated that the signal would be electrical in nature. A search for this revealed that long bones subjected to bending stress did show electrical activity in vitro, the side under compression becoming negative with respect to the side under tension. It was possible to detect the flow of an extremely small current between the two surfaces, the magnitude of the current being proportional to the magnitude of the stress. Since the current flow was primarily unidirectional it was felt that possible classical piezoelectric properties of either the bone mineral or the collagen fibers[3] was not the mechanism of production and we suggested that possibly some stress sensitive semiconducting mechanism was operative.[4]

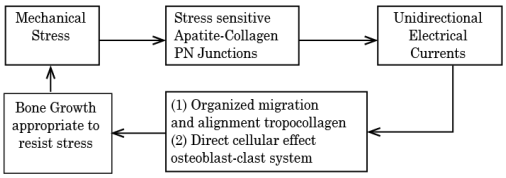
In order for a substance to exhibit semiconducting properties the molecular structure of the material must be crystalline or quasi-crystalline in nature. Electron microscopy has demonstrated that bone is such a highly ordered system, consisting of primarily two components at the molecular scale. The organic matrix consists of collagen fibers lying parallel to each other and roughly parallel to the long axis of the bone. These fibers show the standard 640Å cross striation of native collagen while affixed to the surfaces of the fibers are the minute crystals of bone mineral. These crystals are 200-500Å in length and lie between the cross striations of the fibers with their long axis parallel to the fiber axis. The present concept is that the mineral crystals are most probably hydroxyapatite. In our initial studies we utilized whole bone and were able to show that it exhibited the general properties of a semiconductor; i.e. it could carry small currents, at small

*This material was presented at the Biophysics Seminar, University of Arkansas, College of Medicine, June 4, 1965.

**Chief, Orthopedic Section, Veterans Administration Hospital, Syracuse, New York; Associate Professor of Surgery, State University of New York, Upstate Medical Center, Syracuse, New York.

voltages for long periods of time and the magnitude of the current at any single voltage level was very temperative sensitive. Analysis of the two components separately, revealed that they were both semiconductors but of different types, collagen being an N type (conducting by means of negative charge carriers) while apatite was P type (conducting by means of positive charges).[5] When two such semiconductors are joined together in certain precise fashions a particular device called a PN junction diode is formed. Such structures have certain very specific properties, the most important of which, for our purposes, is a very great sensitivity to mechanical stress with the output of a unidirectional current under such stress. Obviously this is then ideal as the mechanism of stress electrogenesis in bone. We have substantiated this view by demonstrating that bone possesses other characteristics peculiar only to a PN junction diode such as rectification[4] and specific photoelectric effects such as photoconductivity, photovoltaic effect and action spectra.[6] In all of these instances a remarkable similarity was noted between bone and manufactured inorganic PN diodes. We have therefore concluded that mechanical stress applied to a bone produces a proportional electrical signal by virtue of the PN junction diode, produced by the precise relationship between apatite and collagen.

Having now arrived at an appropriate signal and a mechanism to produce it, the next question is, how does the signal produce directed bone growth? Two mechanisms were considered, first that the unidirectional electrical current may be involved in the migration of either mineral ions or elements of the organic matrix and second that the activity of the cellular elements of bone might be influenced by the electrical environment. In the latter case we know that an equilibrium normally exists between osteoblasts building bone and osteoclasts destroying bone, and that each cell type can be converted into the other depending upon certain unknown circumstances. The first possibility was studied initially and tropocollagen was chosen as the possible migratory molecule. Tropocollagen is a filamentous protein molecule about 2400Å long and 14Å side which is known to be an electrical dipole. It is the immediate precusor of the collagen fibers and since the orientation of the bone matrix is basically the result of collagen fiber orientation appropriate migration and alignment of tropocollagen in an electrical field would be most satisfying. Experimentation did reveal such migration, much more satisfactorily in fact than can be explained on a theoretical electrophoretic basis. The molecules of tropocollagen within a solution will migrate under the influence of a very weak electrical current ($<1\mu$A), towards the negative pole but will become stationary at a point ¾ of the way between the negative and positive poles. In this position they line up parallel to each other and *transverse* to the lines of current flow.[5] This position and orientation is precisely identical to that of newly formed collagen fibers in living bone subjected to bending stress! The mechanism responsible for this phenomenon is as yet unknown, however, we do know that all chemical methods of polymerization of collagen from tropocollagen solution produce a random network without parallelly arranged fibers. The migration and alignment of tropocollagen fibers in electrical fields of a strength similar to that produced by stressed bone is obviously one method of producing organized growth. However, this will not produce resorbtion at the positive area, and in order to study this aspect small battery powered devices were inserted into the long bones of dogs. At certain very precise current levels (2 to 10μA between electrodes separated 1 cm.) prolific new bone growth associated with large numbers of osteoblastic cells occurred in the vicinity of the negative electrode. There also appeared to be some resorbtion at the positive pole although at this time this process is difficult to ascess.[7] We may therefore complete our theoretical control system as follows:



The reader is cautioned that this control system is appropriate for the growth response to mechanical stress only, and is not related to either fracture healing or epiphyseal growth (although both of these phenomena demonstrate electrical properties also). The present status of our research does not warrant any clinical application, at this time. In this regard the easily simulated electrical control signal furnishes an ideal site for clinical intervention, however, the author believes that the occasions in which this system will be used to

produce growth stimulation will be few in number. One might better examine the growth retardation at the positive electrode in the light of the extremely poor clinical results from all types of therapy in malignant bone tumors. It is interesting to note that Humphrey & Seal reported in 1959 that low amperage direct currents not only inhibited the growth of unplanted sarcoma in mice when oriented so that the tumor area made electrically positive, but also in a significant number of animals there was complete disappearance of the tumor, and long term survival of the host animal.[8]

Looking beyond the possibilities of imminent clinical application, the identification of this growth control system appears to be of some basic import in the study of growth in living systems in general.

BIBLIOGRAPHY

1. Wolff , J. Das Gesetz der Transformation der Knochen Berlin, A. Hirschwold 1892.
2. Becker, R. O. The Bioelectric Factors in Amphibian Limb Regeneration. Journal of Bone & Joint Surgery *43-A,* 643-656, 1961.
3. Fukada, E. & Yasuda , J. On the Piozoelectric Effect in Bone. Journal of Physiological Society, Japan, *12,* 1158, 1957.
4. Bassett, C. A. L. & Becker, R. O. Generation of Electrical Potentials by Bone in Response to Mechanical Stress. Science, *137,* 1063-64, 1962.
5. Becker, R. O., Bassett, C. A. L. & Bachman, C. H. Bioelectric Factors Controlling Bone Structure. Bone Biodynamics, Frost, H. (ed.). 209-239, Little Brown and Co., 1964.
6. Becker, R. O. & Brown, F. M. Photoelectric Effects in Human Bone. Nature, *206,* 1325-1328, 1965.
7. Bassett, C. A. L., Pawluk, R. J. & Becker, R. O. Effects of Electrical Currents on Bone in Vivo. Nature, *204,* 652-654, 1964.
8. Humphrey, C. E. & Seal, E. H. Biophysical Approach Toward Tumor Regression in Mice. Science, *130,* 388-390, 1959.