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# ELECTRICAL EFFECTS IN BONE

When bone is mechanically deformed, it generates a small electric current. This suggests that the changes that occur in living bone when it is under mechanical stress are mediated by electric fields

by C. Andrew L. Bassett

The most striking characteristics of bone are its solidity and strength. In performing operations on bone the surgeon saws it, drills it, places screws in it, nails it and otherwise treats it like wood. Before the advent of materials such as steel and plastics men used it in a wide variety of tools, weapons and art objects, largely because it was hard and durable. Yet in the living organism bone has another feature that seems the opposite of durability: it is remarkably changeable.

Living bone adapts its structure to changes in mechanical load; like the proverbial twig, as bone is bent, so grows the bone. This property of bone was concisely stated in 1892 by the German anatomist Julius Wolff. In its modern form Wolff's law can be phrased: "The form of the bone being given, the bone elements place or displace themselves in the direction of the functional pressure and increase or decrease their mass to reflect the amount of functional pressure." In other words, bone not only alters its orientation in response to mechanical stress but also gains or loses substance.

How is bone able to achieve these changes? Its capacity is perhaps even more impressive in view of the fact that it is largely composed of hard mineral crystals. Here, however, is a clue to a possible mechanism by which bone shapes itself. Many crystals are piezoelectric; that is, when they are subjected to mechanical stress, they produce an electric current. It seems likely that such electrical effects play an important role in the behavior of bone—even though it now appears that the mineral crystals of bone may be only secondarily involved in them.

Let us consider the behavior of bone in a little more detail. In a child any long bone, such as the thighbone, can be fractured completely and yet can heal even when the two sides of the break are not precisely aligned [*see illustration on page 4*]. After the fracture a mass of reparative tissue grows across the break, setting the stage for osteogenesis: the formation of new bone. The reparative tissue—which may contain cartilage, connective tissue and fibers of new bone—is called a callus. The new bone is formed by specialized cells known as osteoblasts; at the same time it is trimmed and shaped by bone-destroying cells, the osteoclasts. (A third type of cell—the osteocyte—is found inside the bone in the tiny spaces called lacunae, where it serves to maintain normal bone tissue.) After the healed bone has been in use for a year or two, the site of the fracture will probably be impossible to distinguish on an X-ray plate.

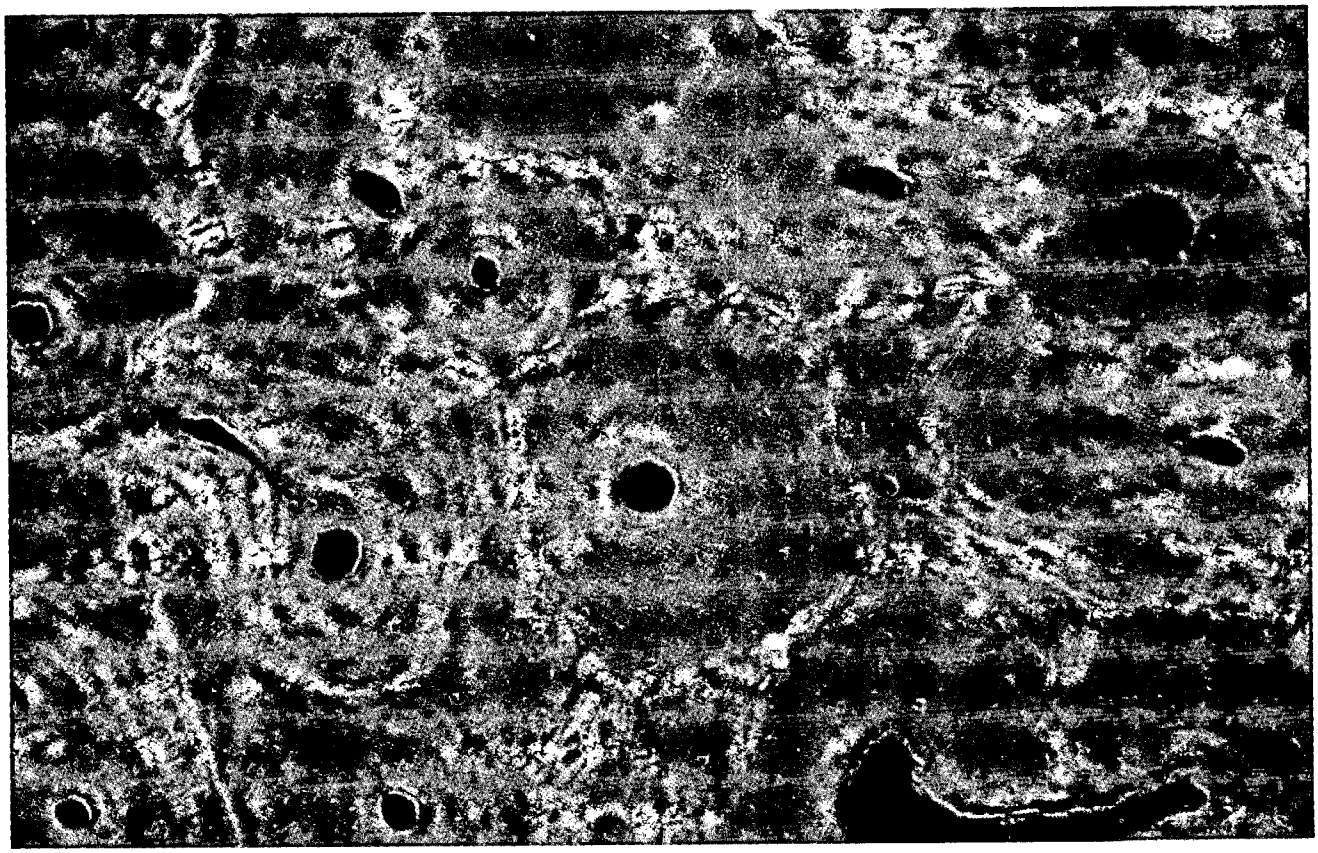
The question is: What is the nature of the stimulus that induces the formation and destruction of bone exactly where these processes are needed? Or, to put the question in a more general form, what is the signal for change in bone? A number of laboratories have undertaken to look into the matter, among them our Orthopedic Research Laboratories at the Columbia University College of Physicians and Surgeons and those of E. Fukada at the Institute of Physical and Chemical Research in Tokyo and I. Yasuda at the Second Red Cross Hospital in Kyoto.

A concept basic to such investigations, as it is to many other investigations in modern biology, is that of negative-feedback control. Here the negative-feedback control system consists of (1) a signal from the environment, (2) a transducer to convert the signal into a meaningful biological response and (3) the response itself. Usually the system also involves (4) a second transducer to translate the response into (5) activity that will correct or stop the original environmental signal. This circular feedback system is said to be negative when it damps the effect of an excessive signal, as opposed to enhancing the effect.

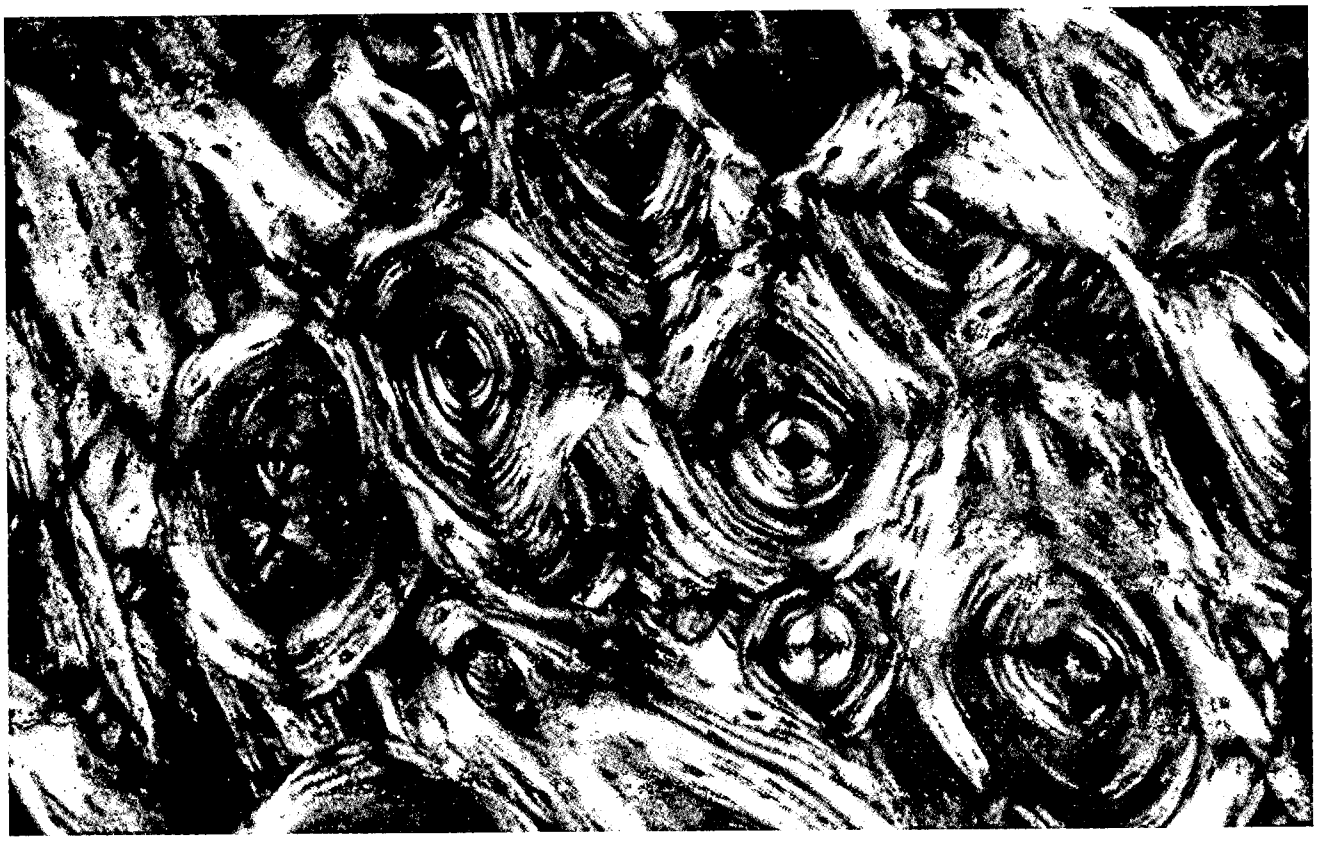
It had been known that a negative-feedback system appears to control another activity of bone: supplying calcium to the blood. Franklin C. McLean of the University of Chicago had pointed out that when the level of calcium ions in the blood plasma fell below a certain point, this gave rise to a signal for the parathyroid glands to secrete greater quantities of hormone. The parathyroid hormone activates the osteoclasts to destroy a certain amount of bone and release calcium to the plasma, thereby eliminating the cause of the original signal [see "Bone," by Franklin C. McLean; SCIENTIFIC AMERICAN, February, 1955].

It now appears that the phenomenon summarized by Wolff's law also represents a negative-feedback system. In this case the environmental signal and the final correcting response were known: a deforming force results in a change in bone structure needed to resist the force. The mechanisms by which one led to the other, however, seemed quite mysterious until the transducers were identified.

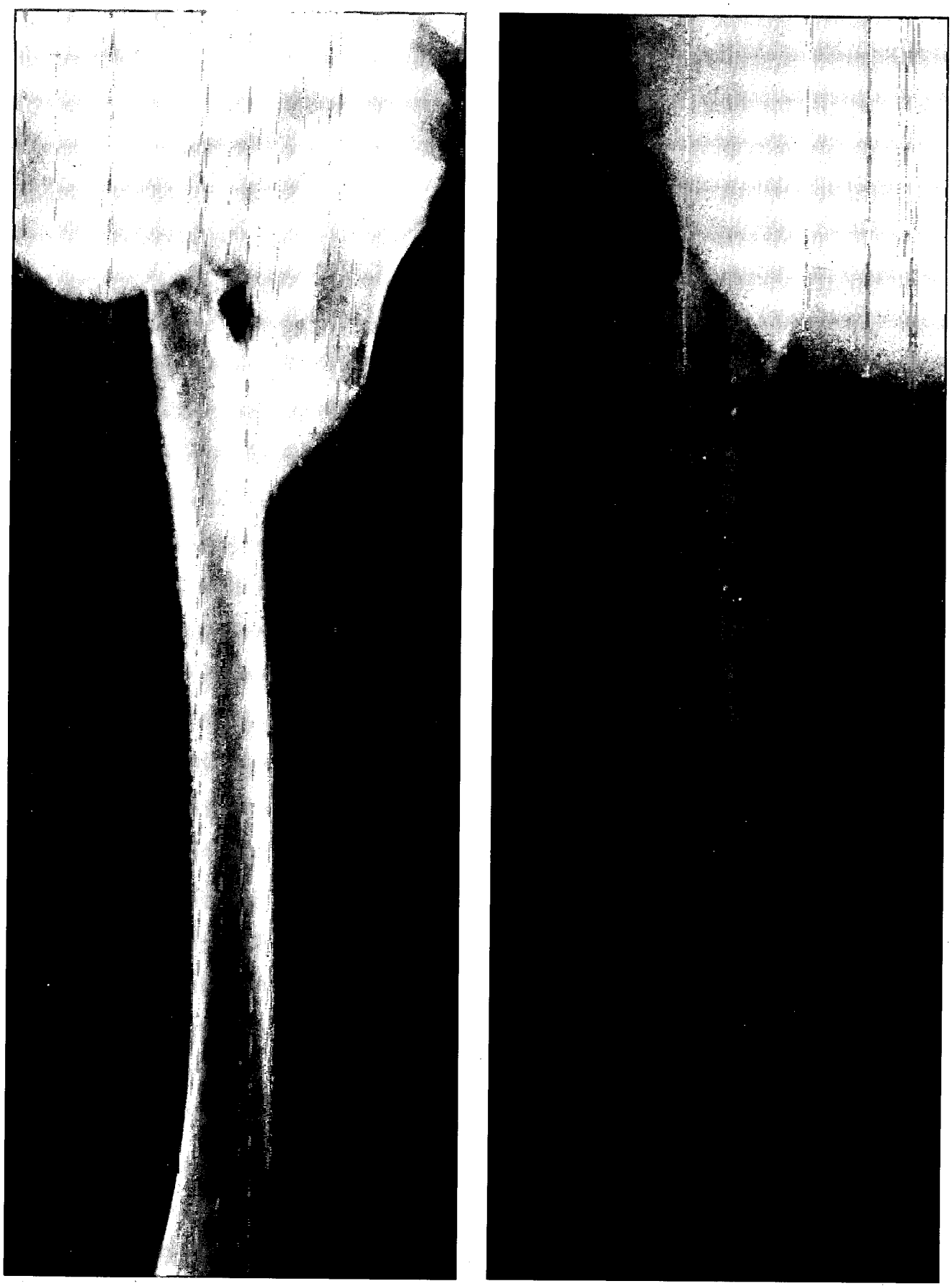
The mineral crystals of bone are embedded in an organic matrix; they account for roughly two-thirds of bone by weight. The structure of the bone crystals closely resembles the structure of fluorapatite, a mineral found in rocks. In the bone crystal, however, the positions of the fluorine atoms in fluorapatite are occupied by hydroxyl groups (OH); accordingly the bone crystal is called hydroxyapatite. The organic ma-



PHOTOMICROGRAPH OF BONE enlarges some 80 diameters the roughly cylindrical units called osteons. Here the osteons are seen end on; each one is represented by a whitish outline. The large dark spot in the middle of each unit is a canal traversed by blood vessels. The smaller dark spots arrayed in circles around the canals are cavities that contain the specialized cells of bone.



POLARIZED-LIGHT MICROGRAPH made at the same magnification indicates that bone is highly crystalline. This is shown by the rings around each canal and also by the dark cross pattern, which is characteristic of certain crystals viewed in polarized light. The rings are made up of crystals of the mineral hydroxyapatite embedded in a crystalline matrix of the protein collagen. The rings are alternately light and dark because the orientation of the crystalline material changes, alternately passing light and blocking it.



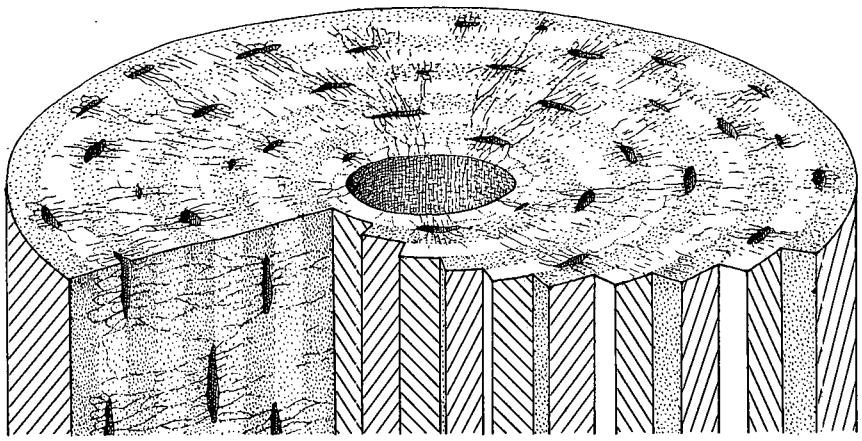
CHANGEABILITY OF BONE is exemplified by the healing of a fracture, depicted in these two X-ray plates. Fractured thighbone of a two-year-old boy appears in plate at left, made in August, 1963, four months after the break occurred. Upper part of bone had been broken off toward right; it was not set, although a cast was placed around the leg to prevent further damage. Callus of connective tissue, cartilage and new bone extends across the fracture gap. In plate at right, made in October, 1964, a year and a half after fracture occurred, the bone has healed and the site of fracture is scarcely apparent. Special cells are trimming the rough edges, and the healed bone is gaining a mass and orientation appropriate to resist normal stresses to which it is exposed.

trix in which the hydroxyapatite is deposited is composed mainly of the protein collagen, and it too is in a crystalline state: its long-chain helical molecules lie side by side in an array that forms a regular hexagonal pattern when it is viewed from the end. Thus bone is made up of at least two crystalline systems.

The fact that bone is so highly crystalline suggested to several investigators that it might be piezoelectric—that it generates an electric current when it is mechanically deformed. In 1953 Yasuda demonstrated that it was indeed piezoelectric; similar observations were made in our laboratory in 1956 and 1957. Later in 1957 Fukada and Yasuda (who were then working together) published a detailed study of bone's piezoelectric properties. They also discovered that dry collagen would develop an electric charge when it was stressed or bent, and this led them to propose that the source of piezoelectricity in bone was collagen.

No evidence has yet been advanced to suggest that hydroxyapatite crystals are primarily involved in the piezoelectricity of bone. There are, however, at least two other systems in bone that may give rise to electric charge. First, the organic matrix in which hydroxyapatite crystals are embedded contains not only collagen but also hyaluronic acid, a long-chain molecule of the class known as mucopolysaccharides; recently it has been found that when certain members of this class of molecules are deformed, a separation of the electric charges in them occurs. Second, work by R. O. Becker at Syracuse University suggests that the interface between collagen and hydroxyapatite is a semiconductor junction of the *p-n* type: a junction between two crystals in which the relative availability of electrons is different. Crystalline collagen tends to have an abundance of electrons; crystals of hydroxyapatite, a lack of them. Bending a *p-n* junction between the two would generate an electric potential. In short, electricity theoretically could be generated in bone in any or all of three ways: a stress on or bending of collagen fibers, a bending of mucopolysaccharide molecules and a stress on the collagen-hydroxyapatite interface.

Becker, together with C. H. Bachman, has analyzed the electrical properties of bone in an effort to determine which of the mechanisms actually operates. His studies indicate that these properties are not simple enough to be explained by the usual piezoelectric effects encountered in one kind of crystal. His view is disputed by, among others, Morris H. Shamos and Leroy S. Lavine of New York University, who believe that collagen alone is probably the main source of stress-induced potentials. The investigations in our laboratory, however, tend to substantiate Becker's view in that they suggest that the source of electricity is a multitude of tiny junctions between collagen and hydroxyapatite.



**STRUCTURE OF OSTEON is shown in three dimensions. In the middle is the canal that contains the blood vessels; it is connected by much finer canals to cavities that contain osteocytes, the cells that maintain the bone tissue. The concentric layers are composed mainly of hydroxyapatite embedded in variously oriented fibers of collagen (*colored lines*).**

In a series of experiments designed to clarify the matter, strips of bone of various widths were gradually deformed while the electricity generated in response was measured. At a certain point, known as the plastic range, the bone will not completely spring back from its deformed position. We observed that, until the plastic range was reached, bone strips of all widths generated electricity roughly in direct proportion to the amount of deformation they had undergone. Thereafter the rate of increase of electrical output dropped—most markedly in the thicker specimens, which reach the plastic range after significantly less deformation.

When we chemically removed the hydroxyapatite from the specimens, however, the amount of electricity generated by deformation was much less. This suggests that collagen alone cannot be the main source of electric charge. In this connection it is useful to regard bone as a two-phase material, one phase being hydroxyapatite and the other collagen. (Actually bone is a three-phase material if we include the substances that appear to cement the hydroxyapatite crystals together.) In such materials, a nonbiological example of which is fiber glass, a strong but brittle substance is embedded in a weaker but more flexible one; the combined substances have a greater strength for their weight than either substance alone [see "Two-Phase Materials," by Games Slayter; SCIENTIFIC AMERICAN, January, 1962]. In bone, of course, hydroxyapatite is the stronger material and collagen the more flexible, and bone's modulus of elasticity lies between that of the mineral and that of the protein. Accordingly collagen probably cannot be flexed enough to give rise to the observed potentials. A significant stress would be likely to develop, however, at the junction between the collagen and the hydroxyapatite when bone is deformed.

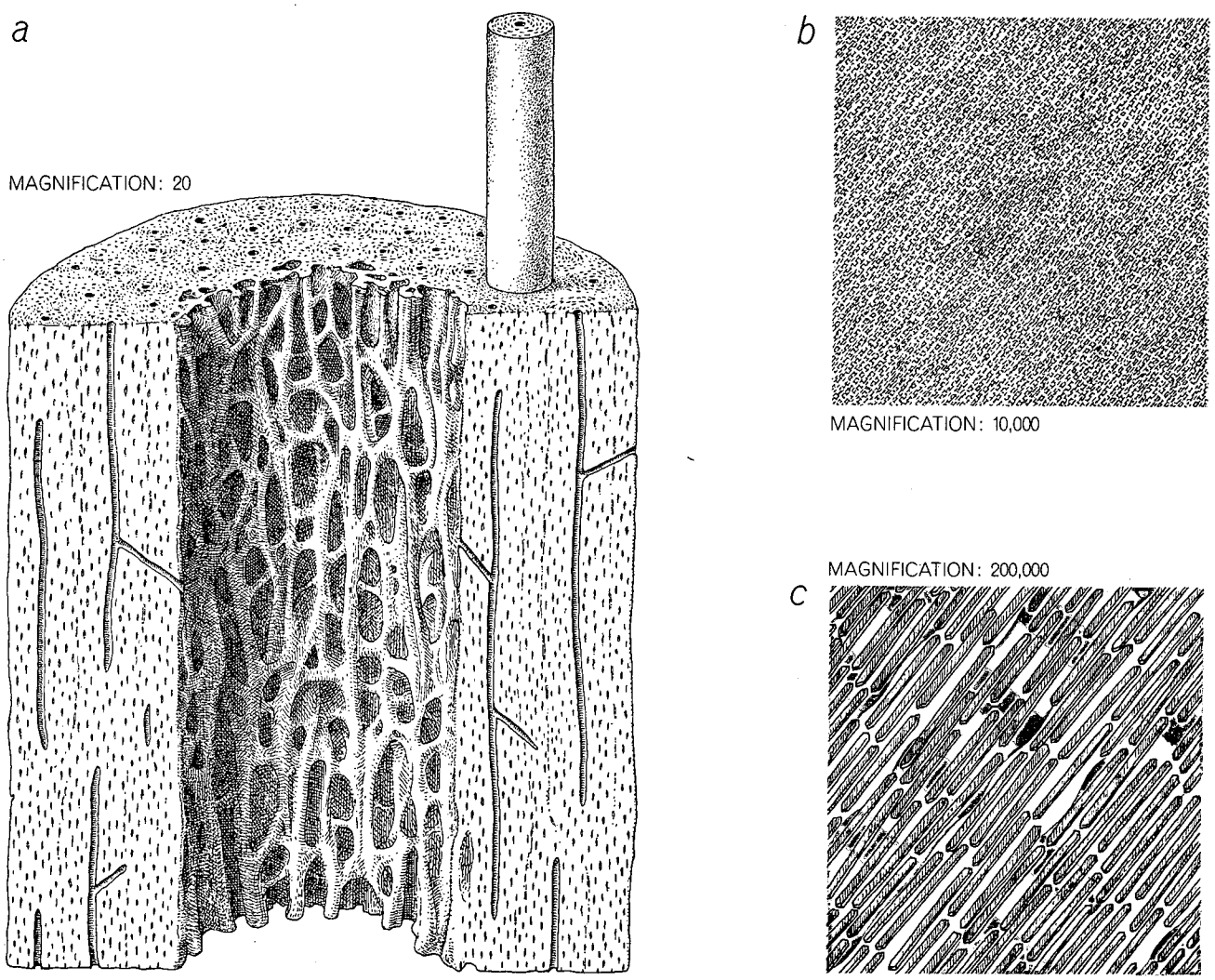
Now let us consider the role electrical effects are likely to play in the feedback system that regulates change in bone. Four of the five elements in our generalized negative-feedback system can be identified. The initial environmental signal is a deforming force. It activates a large number of piezoelectric transducers, which generate electric potentials proportional to the applied force. In order to change the architecture of bone so that in time it can resist the force, the potentials must stimulate a second transducer mechanism. If the original force is compressive, that is, if it is directed along the axis of an existing bone structure, the change may involve only an increase in mass; if the force acts at an angle to the axis, giving rise to shear, the modifications will involve realignment. In 1962 Becker and I postulated that electric potentials not only affect the activity of bone cells directly but also influence the pattern in which large molecules such as collagen come to-

gether. Our investigations since then have generally confirmed these postulates. We have found that formation of bone in living animals can be influenced by weak, artificially induced direct currents and that the alignment of collagen molecules in solution outside the body can be influenced in much the same way.

When drops of collagen in solution were subjected in our laboratory to a current comparable to that calculated for living bone responding to deformation, in from one to five minutes a band of collagen formed at right angles to the direction of the electric field (and near the negative electrode). The collagen molecules in this band could be made to form fibers by the addition of salts of the appropriate ionic concentration. Once the fibers had formed they remained stationary after the current had been shut off; they were found to be parallel to one another and perpendicular to the lines of force of the electric field in which they had developed. The bands formed more rapidly when we used an intermittent current rather than a continuous one. Although it was not surprising that the electrically charged molecules of collagen migrated in an electric field, it was most interesting that they moved so rapidly and formed such an orderly pattern under the influence of currents as small as those we were using.

On the basis of these results in vitro it seemed possible that molecules with a net electric charge could migrate and align themselves under the influence of currents of the magnitude found in vivo. Such behavior may have far-reaching biological significance. If the long-chain molecules manufactured by living cells are piezoelectric, they may possess an automatic control mechanism when they are outside the cell. When they are deformed, they may produce an electric charge that can selectively attract, repel or align charged molecules and ions in their immediate vicinity.

Here the precise nature of the electrical signal produced in living bone is of central importance. For example, if the signal is a wave with positive and negative phases of equal amplitude, an electrically charged molecule would merely move back and forth as the wave passed. There is an exception to this statement: if, as one phase of the wave passes, the molecule is chemically linked with another, it may not be able to move back when the second phase passes. On the other hand, the signal may not be a wave with two equal and opposite phases; one of the two phases may be dominant or there may be only one phase. In that case it would not be necessary to invoke the exception in



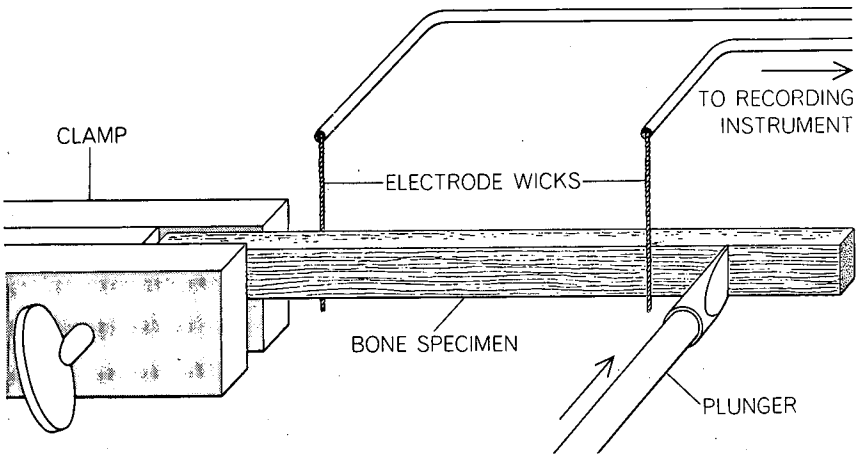

**FINE STRUCTURE OF BONE** is illustrated on three levels of magnification. At left (*a*) is a section of bone depicted without its inner marrow. Haversian canals oriented on the long axis are the main branches of the circulatory network in bone. One osteon is shown extending from bone to emphasize its unit structure. At top right (*b*) section of osteon is shown to consist of collagen fibers (*color*) and hydroxyapatite crystals (*gray*). At bottom right (*c*) juxtaposition of collagen and hydroxyapatite is rendered in detail.

order to show that the signal can move a molecule in one direction to form bone.

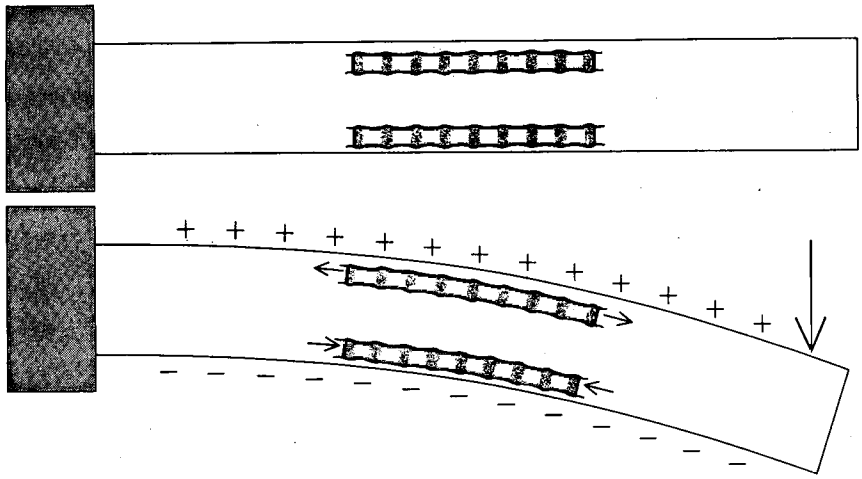
What must the electrical signal actually achieve to build bone? The fundamental structural unit of bone is the osteon: a cylinder with a central canal traversed by blood vessels. Around the canal are concentric lamellae, or thin layers, of hydroxyapatite within and around highly organized bundles of collagen fibers; the lamellae are penetrated by smaller canals [*see illustration on opposite page*]. The regularity of this repeating unit implies that its construction involves a very precise control system. Such a system must obviously do more than simply influence molecules to move into position; it must also organize the activity of such cells as the osteoblasts and the osteoclasts. This idea is not farfetched; there appears to be a close relation between the electrical characteristics of the living cell and its external electrical environment.

In our laboratory we have shown that the nature of the electrical pulses obtained from bone varies significantly with the rate, magnitude and duration of its deformation. The orientation of osteons, lamellae, canals or mineralized bundles of collagen with respect to the direction of the applied force can also affect the character of the pulse. Moreover, it is likely that the relative degree of mineralization or hydration in various parts of the bone will affect its electrical behavior. The actual generators of electricity are so small that it is not possible to measure their individual activity; the pulses recorded in these studies must therefore represent the summation of billions of individual events occurring within the specimen under investigation.

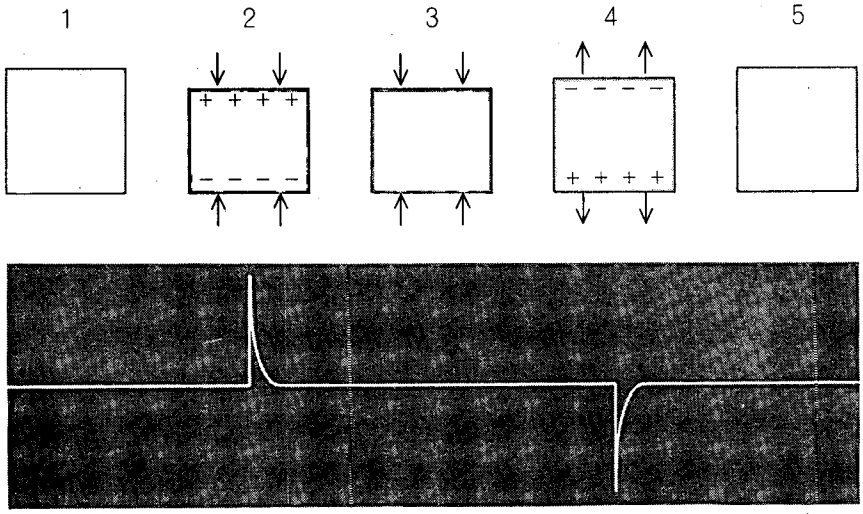
Even though these considerations influence such characteristics of the electrical signal as magnitude and decay time, we have found in our laboratory a uniformity in one feature of the pulses obtained by deformation: their polarity. Regions under compression, which tend to be concave, are usually negatively charged; regions under tension, which tend to be convex, are usually positively charged. It is known both clinically and experimentally that a concave region of bone will be built up and a convex region torn down. This observation led to the prediction that electrically negative regions are associated with the building up of bone and the positive regions with its tearing down. With this prediction in mind we




**DEFORMATION EXPERIMENT** to measure the current produced when bone is bent is diagrammed. A thin, moist strip of bone is placed in an insulated clamp at one end and bent by an insulated plunger at the other. Two electrode wicks are attached to bone, one on each side, an inch apart. Current generated in the bone is recorded on an oscilloscope.



**POSSIBLE EFFECT OF DEFORMATION** on bone is depicted. In strip at top collagen fibers are represented in normal alignment. Strip at bottom is bent so that collagen fibers stretch on one side, are compressed on the other. As a result shear stresses develop between adjacent strands of collagen and opposite charges build up on opposite sides of the unit.



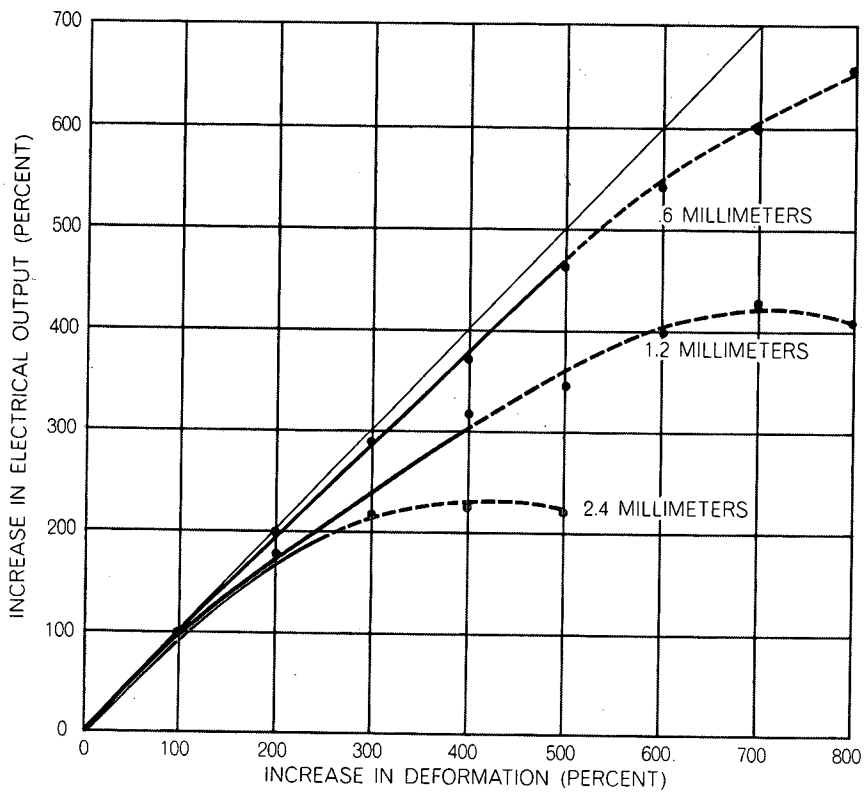

**PIEZOELECTRIC EFFECT** caused by stress on bone is illustrated. Each rectangle represents a piezoelectric crystal which, when compressed (*2*), produces an electric charge that tends to "leak" (*3*). When stress is removed (*4*), crystal resumes its original shape and charge is reversed. These steps give rise to oscilloscope trace of shape shown at bottom.

observed the effects on living bone of artificially induced continuous direct currents. We implanted a small, painless battery pack in the thigh of each of several dogs so that two platinum electrodes projected into the marrow space. For purposes of experimental control we inserted inactive batteries in some of the dogs; these dogs developed small masses of new bone at the point where each inactive electrode projected into the marrow space. In those dogs carrying active batteries a larger mass of new bone formed only around the negative electrode. Similar results have been reported by Yasuda in Japan. Surprisingly in our experiments there was no erosion of bone around the positive electrode.

How can this partial refutation of our prediction be explained? The dogs were active after the electrodes were inserted, and strong stresses were probably developed in the region of both holes in the bone. Such concentrations of stress might have caused an increased electrical activity of the bone itself that overrode the local effects of the artificial positive electrode. On the other hand, a simple connection between positive charge and bone destruction may not exist. The experiment nonetheless demonstrated that bone growth is enhanced in regions of negative charge. The effect of artificial continuous currents did not, however, establish a conclusive link between stress-induced potentials and the activity of bone cells.

All the evidence so far indicates that the intermittent electrical signals measured on bone surfaces have two phases; that is, the signal first has one polarity and then the other. It thus seems reasonable to ask: Can a cell discriminate between the positive and the negative phases of the signal and act accordingly? Or does it react to the greater or lesser electrical activity produced by greater or lesser stress? Although concrete answers are not yet available, one can put forward a working hypothesis. Such a hypothesis should explain how bone cells can simultaneously specialize as osteoblasts and osteoclasts even when they are only a few thousandths of a millimeter apart.

Generally speaking, to detect a difference in electric potential means to measure the relative availability of electrons or certain ions. One might put forward the hypothesis that bone destruction results when electrical activity is diminished or nonexistent. This line of reasoning can lead in any one of several directions, but here I shall take up only one of them.

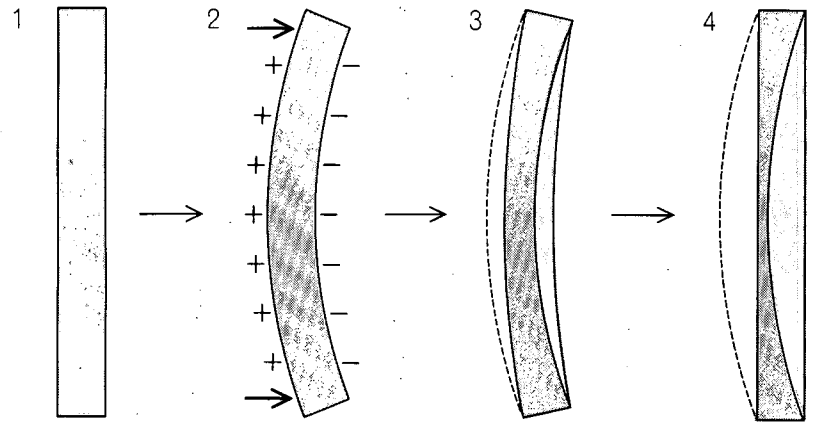



**ELECTRICITY GENERATED BY DEFORMATION of bone is graphed by plotting increase of electrical output in percent (*vertical axis*) against the increase in deformation in percent (*horizontal axis*) for bone strips of several widths. The straight line represents an ideal linear, or one-to-one, relation. Broken lines indicate that bone strips have been deformed to the plastic range, that is, the point beyond which the strips will not spring back to normal. In this range there occurs a diminution in the rate of increase of electrical output.**

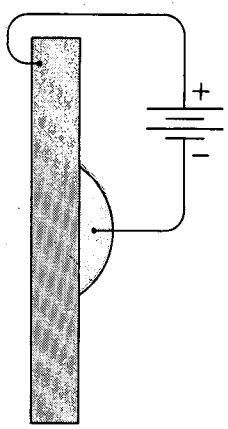
Tissues are nourished by the movement of fluids, and bone is no exception. Obviously, however, the movement of fluids through bone presents difficulties. Bone is almost incompressible under normal loads, so that fluids cannot be "massaged" back and forth. The tiny canals in the bone through which the fluids must move account for only 3 percent of the area in a cross section of bone tissue. Furthermore, many of the bone-tending osteocytes are situated at relatively large distances from blood vessels. In view of the inefficiency of this supply line, it might be expected that most osteocytes would be on the brink of starvation for nutrients or oxygen. Under the stimulus of minor, normal deformations of the skeleton, however, an alternating electrical signal could act as a pump to promote the ebb and flow of ions and charged molecules. If such a pumping system exists (and if it does not, the nutrition of bone cells remains a mystery), it may depend on the junctions between hydroxyapatite and collagen. There are approximately a billion of these possible generators of electricity around each osteocyte.

If the generation of current were increased above normal levels in a given region, cells in the region might be activated to produce bone and stabilize the region. Conversely, diminished electrical activity might result in the death of osteocytes by starvation. It should be emphasized that the potentials generated by stress apparently do not require the presence of living cells. Bone in the body that has lost its living tissue may continue to generate potentials if it is intermittently deformed; thus it may escape destruction by osteoclasts.

If osteoclasts appear in regions where the electrical signal is diminished or absent, it should be possible to find a common electrical link between the factors known to cause bone destruction. For example, although it has been said that bone destruction requires a local increase in the number of blood vessels, it is not clear whether the increase occurs before the destruction or after it. If, as one investigator believes, the increase in the volume and rate of blood flow called active hyperemia causes



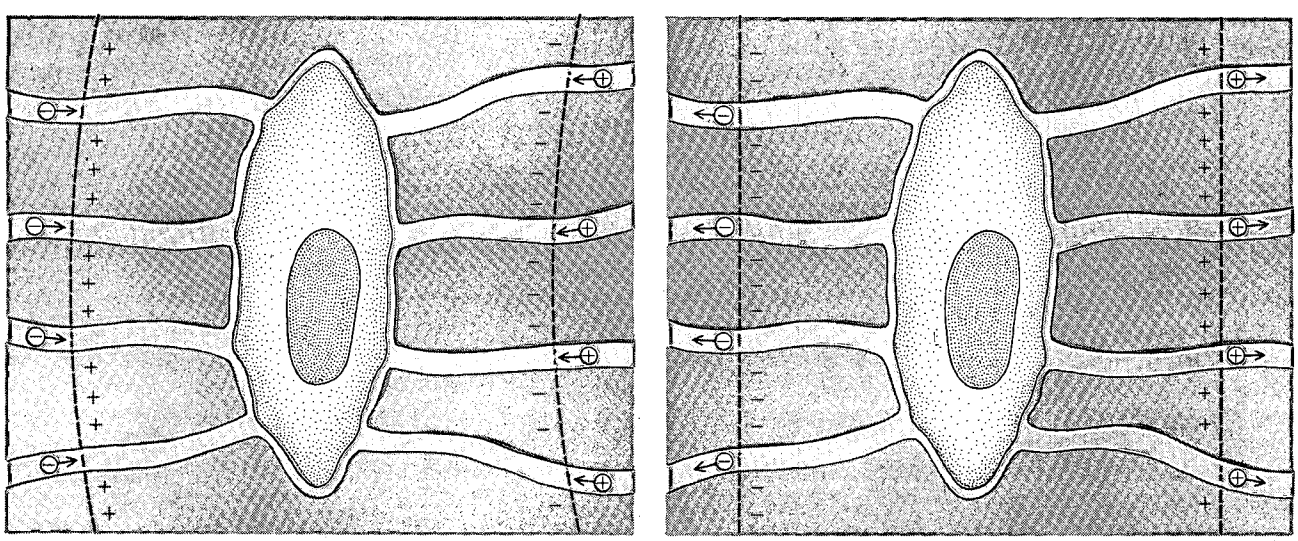

NEGATIVE CHARGE AND BONE GROWTH were associated by observing normal response of bone to deformation. When negative charge builds up on concave side (*2*), new bone forms to fill it and old bone is removed from convex side (*3 and 4*) to straighten it.



ELECTRIC CURRENT applied to undeformed bone caused growth in area of negative charge, no loss in area of positive.

bone destruction, it might do so by providing more oxygen molecules to act as electron "sinks." Furthermore, arteries are positively charged on the outside and negatively charged on the inside. It is therefore conceivable that the erosion of bone by the abnormal enlargement of an artery may be electrically mediated, because the larger vessel could conduct away more electrons. Finally, a recent observation that the hormone of the parathyroid glands influences the electrical conductivity of cell membranes lends support to the idea that bone destruction is controlled by electrical effects.

It appears more than likely, then, that changes in the orientation and mass of bone are controlled by stress-generated electric potentials, even though it is far from clear exactly how these potentials achieve their effects. If this is true, electrical effects are obviously important not only in situations such as a broken bone but also in many other pathological conditions affecting the skeleton. Bone may function as an exquisitely sensitive piezoelectric gauge, responding to the slightest jar or deformation. There are several sources of normal mechanical input for the skeleton. The cardiovascular system provides a continual deforming force by means of hydrostatic pressures in the blood vessels, and possibly through the recoil of the heart. Gravity causes direct distortion of the skeleton, and it stimulates the tone of the muscles that must stabilize the body against gravity; the intermittent pull of these muscles also deforms the bone. When a voluntary muscle action—such as a stride—is taken, additional mechanical stress is developed; with each step the shock from the impact is transmitted throughout the skeletal system. These sources of mechanical stress have some relevance to space travel. The astronaut who is subjected to prolonged periods of weightlessness loses the major portion of mechanical stimuli to bone, and must therefore expect his bones to lose mass at a more rapid rate than those of a person who must remain in bed or otherwise inactive for a protracted period. On the other hand, cardiovascular activity may suffice to provide the minimal stress that produces a threshold electric signal in bone—the signal that keeps the feedback system in operation.



ELECTRICAL EFFECT ON BONE CELLS is outlined according to a hypothesis suggested by the author. A slight stress on bone (*left*) might generate an electric charge that attracts or repels electrically charged molecules and ions in the blood plasma bathing the osteocytes. Removal of stress (*right*) would cause reversal of charge and an opposite effect on charged particles. This electrical pumping system would explain how nutrients in the blood are passed through tiny canals to osteocytes deep within the bone.

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