Letters to the Editor

Bioelectric Effects In Tissue

Dear Sir:

A recent paper by Shamos and Lavine published in *Clinical Orthopaedics*[9] criticizes the thesis of Becker *et al.*[1-4] that the apatite collagen relationship in bone is a stress sensitive, semiconducting PN junction which produces electrical signals when bone is subjected to mechanical stress. They propose instead that such signals are produced by the relatively simple, classic piezo-electric effect in collagen described by Fukada and Yasuda.[6] We will attempt to clarify our position and to point out some defects in their thesis.

Experimental data presented by Shamos and Lavine is limited to determinations of: dielectric constant, resistivity and surface ionization energies for bone as well as a number of other mineralized biologic tissues. They conclude from this data, "There is no compelling evidence of any special semiconducting or rectifying properties in these materials." This conclusion is inappropriate because not one of these parameters has any special characteristics permitting the distinction between a semiconducting and an insulating solid. For example, the authors state, "There is no rigid rule that distinguished an insulator from a semiconductor on the basis of resistivity," yet they then proceed to make such a distinction. In actuality, the distinction between an insulator and a semiconductor is based on the band theory of solids. Insulators have valance bands completely filled with electrons and conducting bands completely empty. In this case, no electrical current will flow through such a solid when a low-voltage electrical field is applied to it.

In semiconductors, on the other hand, excess electrons or holes have been added to the solid in numbers that are appreciable though small compared with the total numbers of atoms present. Some of these charge carriers are in the conduction band, and others can be activated into the band by a variety of means, including light and heat. This property results in the appearance of a steady electrical current through such a solid when a similar electrical field is applied. This current will change considerably in magnitude with relatively small changes in temperature of the solid.[5,7] Therefore, the important criteria for a semiconductor are: the passage of a small but detectable current at low-voltage fields and marked changes in the magnitude of this current with small changes in temperature. We have presented data indicating that a segment of completely dried whole bone with cross-sectional area of 0.5 cm.^{2} will pass a current of 1×10^{-12} amperes at a field of 1.35 volts.[4] Shamos and Lavine's own paper presents data supporting the second criterion (see their Fig. 2). The slope of the curve of conductivity versus temperature enables one to deduce the approximate activation energy (i.e., the energy in electron volts to move one electron from the valance band to the conduction band), and Shamos and Lavine calculate the value of this for whole bone to be about 2.4 electron volts. They deduce therefrom that bone "might be considered as an intrinsic semiconductor," but that it would not display typical semiconductor effects except perhaps at very high temperatures. From the calculated value, the authors deduce further that no activation effects could occur at body temperature and, furthermore, since the reported values for most other proteins lie within the same range,

that doubt may be cast upon semiconductor theories involving all such biologic materials. We feel that it is important to point out that heat is not the only mechanism of activation for semiconductors and that Shamos and Lavine's viewpoint totally overlooks the extensive literature dealing with other activation and energy transfer mechanisms.[10] Furthermore, we feel that it is inappropriate to apply the criteria of inorganic semiconductor technology (for industrial purposes, etc.) to biologic systems with semiconductor characteristics. Bone may be a poor semiconductor material for a transistor in a pocket radio yet may have exactly the most desirable characteristics to function within the living system.

In the discussion of the piezo-electric theory of bone electrogenesis, the 2 key questions appear to be: (1) What sort of electrical signals may be expected from bone subjected to alternating stress and release under experimental conditions? (2) Can the expected electrical activity have anything to do with the growth of bone resulting from applied mechanical stress? Here, we find Shamos and Lavine in an anomalous position. In their present paper, they attempt to prove that unidirectional signals may be obtained from classic piezo-electric materials. Yet, in their initial publication[8] they stated, "Sudden application of a static force resulted in a potential difference between the two electrodes proportional to the stress and with a decay time of about 0.5 sec. . . . On releasing the stress the same voltage pulse appeared with opposite polarity," an obvious description of a bidirectional signal. They attribute to us "the main argument favoring their rectifier model the fact that an alternating signal is produced by application and release of stress in bone." This is not true. We proposed the rectifier system because we did *not* observe a pure alternating signal under these conditions.[1-4]

It is clearly implicit in the term "rectifier" that some device is present to change alternating current to some type of direct current. This concept is well understood by even the most unsophisticated electronic technician. Our view[1-4] is that classic piezo-electricity produces alternating signals on stress and release of stress while a stress sensitive PN semiconductor will produce a unidirectional signal under the same circumstances. It is true that the relationship between the resistance of the sample (R′) and the resistance of the measuring circuit (R) will determine the shape of the observed voltage pulses on stress and release. However, since the voltage is produced by an electric current flowing through the measuring resistor, the same amount of charge must appear at both stress and release. Therefore, the *area* under the voltage curves must be equal for both stress and release. An inexcusable misrepresentation of our data is their implication that the voltage curves presented in our original publication[1] resulted from a situation in which R exceeded the value of R′. It was stated in that publication that steady state potentials were observed with values of R as low as 1×10^6 ohms.[1] This value is 6 orders of magnitude less than Shamos and Lavine's published values of R′ (1.7×10^{11}, 1.2×10^{12} ohms). In our experiments, a greater total current was observed during the application of stress than during the release of stress, and it was noted that the simple, classic piezo-electric theory was inadequate.

In addition, Shamos and Lavine's paper contains a discussion of how the classic piezo-electric effect could be related to bone growth by producing a net migration of Ca^{++} ions to areas of stress. In our view, the classic piezo-electric effect, having alternating positive and negative current pulses, would produce no net movement of charged particles. A further defect in this hypothesis is that since collagen is the prime source of the piezo-electric effect (Fukada and Yasuda demonstrated it with ox Achilles tendon), then Shamos and Lavine's thesis should apply to other organized collagenous structures as well as bone—a circumstance that would lead to the ossification of all organized tendons in the body.

The semiconduction hypothesis at first glance may appear to be more complex than

the piezo-electric hypothesis. However, the concept that collagen is an N-type semiconductor and apatite a P-type and that the precise relationship between the two produces a PN junction (with the normal rectification properties of such a device) is no more complex than the ultrastructure of bone itself. Of course, the major distinction between bone and tendon is that the former is, viewed very simply, a 2-phase system of a collagen matrix plus a mineral microcrystal while the latter is simply collagen. Any theory of the electrogenesis of bone should take this anatomic fact into consideration. Space does not permit a complete review of the data that we have gathered to support our hypothesis. We conclude that bone is a complex semiconductor, and that the ultimate unit of it is the PN junction formed by the precise structural relationship between the collagen fiber and its attendant apatite crystals.[1-4]

The semiconduction theory lends itself well to the development of a feedback control system governing Wolff's Law with growth or resorbtion of bone being dependent on the polarity (positive or negative) in any particular region.[3] Recently, this has been well substantiated by the publication of in-vivo experiments involving the injection of very small direct (unidirectional) electrical currents into dog femur.[2] Growth enhancement was shown definitely at the cathode, a polarity dependence completely in keeping with our general thesis.

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10. Szent-Gyorgyi, A.: Introduction to submolecular biology, New York, Academic Press, 1960.

The interested reader is referred to our 2 latest publications for further substantiation of our views.

1. Becker, R. O., and Brown, F. M.: Photoelectric effects in human bone, Nature 206:1325, 1965.
2. Bachman, C. H., and Ellis, E. H.: Fluorescence of bone, Nature 206:1328, 1965.