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*ELECTRICAL STIMULATION IN ORTHOPAEDICS: PAST, PRESENT AND FUTURE

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ABSTRACT

The observations that stressed bone yielded an electrical signal and that weak electrical currents could induce callus formation gave birth to a sustained and widening interest in the clinical use of electrical currents and magnetic fields. The question of the physiological significance of the stress-generated signals remains unanswered, but it seems likely that the current-caused callus formation is an irritative response similar to that demonstrated by bone subjected to heat, chemical, or mechanical stimuli. A similar mechanism may underly the magnetic-field effects on bone. The future of electrical stimulation in orthopaedics seems tenuous, and only further progress will insure its role in clinical use.

INTRODUCTION

The modern era of bioelectricity had no precise beginning, but as I reckon it the foundation was built by Albert Szent Gyorgyi and the cornerstone was laid by orthopaedic surgeons in Japan and the United States beginning in the 1950's. My aim is to sketch my view of the evolution of bioelectricity in orthopaedics during the last three decades, and to make a few comments about where the area is headed. What follows is not a comprehensive review, but rather an attempt to delineate the most significant developments — of which I count three. In-depth treatments are given elsewhere (1–3).

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THE PAST AND THE PRESENT

In experiments that began in the 1930's, Kuntscher (4) and others established the existence of a phenomenon known as "callus without fracture." They showed that mechanical, thermal, and chemical factors could initiate an osteogenic response leading to callus formation despite the absence of an actual fracture. Iwao Yasuda, a Japanese orthopaedic surgeon, postulated a common pathway for the stimuli, and he theorized that it was electrical in nature. His idea that an electrical factor was the last step in the chain-of-command that initiated the osteogenic response seems to have come from his observation that bone callus was electronegative compared to more inactive regions. Yasuda made electrical measurements on freshly-removed bone undergoing cantilever bending and observed stress-generated signals that were also present in boiled bones and could therefore not have been due to cellular activity (5,6).

Yasuda called the electric potentials "piezoelectricity in bone," in analogy with the well-known but relatively little studied property of piezoelectricity exhibited by some inorganic crystals. For inorganic piezoelectricity, the question of whether the direct effect (mechanical stress causing electrical signal) or the converse effect (electrical signal causing mechanical deformation) is measured is usually a matter of convenience. In materials containing water and diffusible ions, the choice of the measuring technique has more significance. In such cases, a converse measurement is technically very difficult, and the signal obtained via a direct measurement such as Yasuda's usually contains contributions from non-piezoelectric phenomena.

In 1957, a portion of the ambiguity was resolved when it was clearly established that bone was a piezoelectric material in the classical sense. Heated, air-dried cubes of human and animal femur were shown by the converse method to exhibit a piezoelectric matrix in which $d_{14} = -d_{25} = 2\text{–}3.5 \times 10^{-9}$ c.g.s.e.s.u. were the only non-zero terms (7).

If the common-pathway signal was electrical then, Yasuda reasoned, application of electrical energy to bone ought to produce a callus. It did (5,6): 1 microampere, 1.5 volts, passed for 3 weeks along the medullary canals of rabbit femurs produced a ridge of callus between the electrodes.

Clinical observation has shown that healed angulated fractures eventually became straight via a remodeling process in which bone is resorbed on one side and deposited on the other side. In 1961, to evaluate the possibility that it was an electrical signal generated by the mechanical forces applied to bone that directed the osseous activity, C. Andrew Bassett and Robert O. Becker performed an experiment very similar to that of Yasuda, and they obtained the same result (8). Bassett and Becker also drew an analogy with piezoelectricity but, since the measured signal did not behave like that from quartz — a known piezoelectric — they suggested that at least part of the signal arose from mechanical deformation that occurred at the specific locations within bone where the inorganic and organic phases formed interfaces. In 1962, Morris Shamos and Leroy Lavine measured the piezoelectric effect in a number of different bones and also suggested that the surface charges appearing on stressed bone might be controlling factors in bone remodeling (6). Two years later, Bassett and Becker showed that 1–10 microamperes passed for 3 weeks along the medullary canals of dogs produced a massive bone callus (10).

Thus, by 1964, we knew that bone exhibited endogenous stress-generated electrical potentials of noncellular origin and also that dry bone behaved like a classical piezoelectric material, producing an electrical signal only when the applied mechanical force was in a direction that tended to force the collagen fibers to slip past one another. The mechanism underlying the production of the electrical signal in wet bone remained undetermined, but it was clear that applied electricity could induced callus formation (5,6,10).

During the more than two decades since the discovery of stress-generated electrical signals in bone, investigators have sought to establish their true nature, and

to prove or disprove their role in bone physiology. Cochran provided a detailed picture of the actual electrical signals generated in bone under physiological conditions (11). McElhaney (12) showed how the ultrastructural properties of bone influenced the measured electrical signal from dry bone. Annular rings of bone prepared by making parallel cuts through the shaft of a human femur were loaded in pure compression, and the resulting surface charges on the periosteal surface were found to vary significantly in magnitude and sign. Despite the fact that the ultrastructure and piezoelectric polarization varied from point to point along the bone, there still appeared to be an overall pattern in the measured charges. When McElhaney's charge profile was interpreted to be a signal for osseous activity — growth or resorption depending on charge sign, amount of activity depending on charge magnitude — a coherent change in the bone profile emerged from the data (13). Since a remodeled femoral outline resulted rather than a haphazard picture, the data was suggestive of a physiological role for piezoelectricity. In succeeding years, more was learned. Piezoelectricity in bone was associated with the protein collagen, not the inorganic mineral phase (14). The piezoelectric property changed with age (15) as might be expected in a property that was related to the potential for growth. Piezoelectricity was also demonstrated in fully hydrated — but frozen — bone and tendon (16). Freezing the samples removed the technical impediments and made possible measurement of the piezoelectric effect via the converse technique. This measurement seemed to make the existence of piezoelectricity in bone under true physiological conditions more plausible because in view of the known stability of collagen, it seemed unlikely that an increase to physiological temperatures would produce structural changes so drastic as to destroy the piezoelectric property. On the other hand, piezoelectricity in bone was found to be unrelated to audoinduction — the ability of chemically-treated bone to induce an osteogenic response when implanted in a host (17). Since the piezoelectric constant of the treated bone did not correlate with

its ability to produce an autoinductive response, the data suggested that, at least in this form of bone growth, piezoelectricity was not significant. And so it has gone for more than 20 years. There have been hints that piezoelectricity may have a role in bone metabolism, but there have also been suggestions to the contrary. No one has penetrated to the heart of the matter and designed an experiment that unequivocally resolved the issue. Although, in the 1960's, the answer seemed almost within our grasp, it has not materialized, and thus remains one of the fundamental problems in bioelectricity.

In contrast to the failure to solve the riddle of biological piezoelectricity, success was achieved in the clinical practice of electrode-delivered electrical energy. Zachary Friedenberg and Carl Brighton solved the basic problems attendant clinical application of electrical currents in 1971 (18), and by 1981 they had achieved an 83.7% success rate in treating non-unions with 4 20-microampere cathodes (19). The technique received FDA approval and was marketed in the United States (Quadpack, Zimmer) beginning in the late 1970's. Other investigators also reported clinical success, notably Lavine (20) and Becker (21), but of all the systems devised to facilitate introduction of electricity into clinical orthopaedics (22), only one other persevered and reached general use (Osteostim, Telectronics).

The biological significance of stress-generated potentials and the clinical role of electrode-delivered electricity are two of the main threads of the evolving fabric of bioelectricity in orthopaedics. The third thread originated with Arthur Pilla. It appeared for the first time in September, 1973, at a conference on electrically mediated growth mechanisms in New York (23) and was discussed in many subsequent publications. Unlike the electrode studies that partly depended on the stress-generated electrical potentials for their underpinning, Pilla's approach was not intended to mimic a naturally-occurring process. He suggested that cell processes such as the ion-binding, the passage of ions through the cell membrane, and changes in the membrane double-layer could be selectively altered by changing the electrical

micro-environment of the cell, and that these changes, in turn, would produce related changes in cell function. The theory required the presence of an electric field in the bulk of the tissue to be treated which he brought about by applying a time-varying magnetic field. The idea was to produce desirable changes, such as growth, while avoiding undesirable changes by judiciously selecting the time dependence of the applied magnetic field. Between 1973 and 1975 Pilla and Bassett appear to have settled on the particular magnetic field that they believed would be most useful clinically. The technique received FDA approval in 1979 (Bi-Osteogen, Electro-Biology), and enjoyed unprecedented initial success in the marketplace because it yielded a success rate comparable to that found with the electrodes, but without the need for surgery (24). The commercial success of the magnetic-field system has been so great that it has cast doubt on the viability of skin-penetrating electrode systems.

THE FUTURE

From the electrode studies, we have learned that — using almost any electrode material that itself is not toxic — 1–100 microamperes (DC and time-varying), 1.5–7.5 volts, produces bone callus in animals and humans. Below the current range no growth occurs, and above it the tissue is destroyed. Thus, the electrode-delivered electrical energy that is capable of eliciting callus formation is non-specific, and at high levels it causes gross tissue destruction. As Kuntcher showed, this is exactly what is found when heat, mechanical, and chemical stimuli are applied to bone. Electricity — at least that used in the electrodic experiments to produce bone callus — must therefore be added to the list of non-specific stimuli that elicit callus formation.

If callus formation with electricity is essentially a controlled irritative response, what are the implications for extension of its use in orthopaedics? Electricity seems to be application to situations involving the re-lighting of a growth response that should have occurred but didn't, and to possibly accelerating a normal growth response such

as fracture healing. Its applicability to non-localized orthopaedic problems and to problems that do not involve callus formation is more difficult to perceive. It will surely be studied with regard to its potential role in regional, systemic, congenital, and genetic diseases but they seem to be less amenable to electrical treatment than the nonunion or the fracture.

Yasuda believed in a common pathway signal to the bone cell itself that was capable of triggering the process that resulted in callus formation. Because it is the most parsimonious explanation, it seems to me to be the best one to explain the observations. It is possible that heat, mechanical force, and various chemicals produce a direct effect on the cell membrane, but I think that scenario is unlikely. Their most immediate impact is probably elsewhere, and I think the same is true for the effects produced by electricity. We therefore can not understand such effects by focusing on the interaction of the currents and the cell itself. Such a system could no more yield an explanation of events leading to electrode-caused callus formation than could a system involving the application of either heat or force directly to a bone cell.

In contrast to the electrode studies, the rationale for the time-varying magnetic fields is precisely that one can understand their effects by studying the interaction between the applied field and the cell membrane. It is too early to tell whether Pilla has opened a new vista in biology by giving us the means to control and modulate cell function, or has simply hit upon another means of producing bone growth. A salient characteristic of most of the magnetic-field studies thus far has been the apparent absence of callus during the healing process at a non-union site. Recently, the unmistakable presence of callus in magnetic-field stimulated nonunions has been shown (25). Although future studies may prove that magnetic fields having specific time parameters produce specific cellular responses, I can find no convincing evidence that such a phenomenon has actually been demonstrated.

The nature of the interaction between electromagnetic energy and biological organisms is unknown. The solution to that problem, not the best technique for growing bone, is our task. Such a solution would have far-reaching importance, and would affect the entire practice of medicine, not only orthopaedics. The question of growing bone in clinical applications involves numerous non-bioelectrical considerations. Not only must electromagnetic energy grow bone, but also the bone must be therapeutic in the sense that it must cure a disease or alleviate a problem encountered by the clinician. To merit use, electromagnetically-grown bone must achieve its effect more reliably than techniques already available to the orthopaedist. If the success rate using standard therapy is, say, 70% and electromagnetic energy offers 71% then the outlook for electromagnetic energy with its wires, meters, and coils, is probably dim. Lastly, the orthopaedist will require a ready-made system which he can prescribe and install, and thus the question of the commercial viability of the system is crucial.

Electromagnetic energy has established a beach-head in orthopaedics, and the task now is to extend its use beyond the area of non-union, simplify the techniques of application so that they will be more attractive to the clinician, clarify the mechanism of action, and prove therapeutic efficacy using controlled clinical studies which unequivocally establish the relative merits of electricity versus standard therapy. Such experiments will tax our ingenuity, technical capabilities, and dedication.

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