Implications of Bioelectric Growth Control in Orthodontics and Dentistry

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Early History

There is a distinct mood of déjāvu (something seen before) in one area of active research in bone growth and tissue proliferation control. In the eighteenth century Luigi Galvani suggested that "animal electricity" may be an essential ingredient in natural life processes. This led to the conception of numerous theories about electrical deficiencies causing and electrical infusions curing diseases. The fact that electricity could be felt, tasted, seen if sparks were produced and smelled if ozone was a by-product, was used to advantage by the late 19th century top-hatted "clinicians." The public was easily deceived by promises of cures from these "gentlemen" of dubious scientific credentials. They submitted their ills to the product of a mysterious black box replete with complex control knobs and shiny brass electrode devices. When electrical treatment for gum boils or gout was prescribed, there was an immediate, sometimes shocking, experience. Usually the voltage and current was too little to kill, but also, unfortunately too callously applied to heal. There was a suspicion about the composition of pills and liniments but electrical "treatments" gave you something for your money. Electromagnets were equally mysterious, and a separate but similar cult of magnetic healers emerged. They used electromagnetic forces as a remedy or to produce a state of animal magnetism (hypnosis) to alleviate suffering. Certainly hypnotism did bring about palliative effects. Some healers believed that they could generate a personal magnetism (self hypnosis) which gave them insight into the cure of disease. Daniel David Palmer, the discoverer of chiropractic, was such a man. In his text he stated, as a man gifted with extraordinary spiritual insight, "I am the originator, the Fountain Head of the essential principle that disease is the result of too much or not enough functionating (sic) . . . It was I who combined the science and art and developed the principles (of chiropractic). I have answered the question —what is life?"[1,2] Because of such claims, black box charlatans proliferated, eventually failed, and buried Galvani's idea in the dust of quackery.

In the first half of the twentieth century scientists measured the electrical activity of living tissue, and focused on the nature of the electrical output. They developed the boundaries of the norm and some limited application of these observations. For example, in 1903 Mathews[3] discovered that hydroids, a living invertebrate, have an electrical polarity, a natural electret phenomenon. This observation led Lund[4,5] to publish a series of classical experiments that demonstrated that control of polarity by application of a critical amount of current per unit area can induce internode (primitive limb) regeneration. Only repeated confirmations and variations on these experiments appeared in the literature through the early 1950's. This type of research intensified in both amount and sophistication as the post World War II electronics industry evolved. Highly sensitive electrometers, oscilloscopes and other devices enabled scientists to investigate the generation of minute phys-

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iological currents from all varieties of living tissue.

Modern Research

Within the last two decades this new technology was applied in the study of the electrical activity of bone. In 1955 Yasuda[6] and his co-workers explored the electrical nature of callus formation in bone. They found that callus could be produced *in vivo* from controlled mechanical compression of bone or from the passage of low amperage currents between two electrodes placed on a bone. They hypothesized that mechanical stress on bone led to dynamic energy being converted (transduced) to electrical energy which, in turn, played a direct role in callus induction. Fukada associated with Yasuda to demonstrate the generation of a piezoelectric potential from the deformation of dried bone.[7] The character of this potential and small current was extensively investigated and reported by Bassett and Becker *et al.* Their early studies indicated that electrical behavior of bone was analogous to the solid state p-n junction phenomenon.[8,9,10] Shamos and Lavine[11] disagreed with this viewpoint and observed that the stress potential was related to angular stress of collagen contained in soft and hard tissues. The amplitude of the potential appeared dependent upon the orientation of the stress as related to collagenous fiber alignment. They argued strongly that the generated potential probably fitted the piezoelectric model.[12,13] Braden *et al.*[14] as well as Fukada and Yasuda[15] joined the scientific debate and concluded that the piezoelectric activity of hard tissue is dependent upon its collagen content.

Pure mineral apatite and dental enamel show practically no stress generated potential. Electrical potentials increase when an oriented shearing force is applied to matrix-bound hard tissue. This force distorts the cross linkage of long chain "fibrous" molecules. The relationship between bone matrix-fiber direction, applied stress and the resulting surface potential was investigated by McElhaney.[16] Collagen fiber orientation is extremely variable because of bone surface irregularities. Generalizations about charge distribution are difficult to make because of the varying measurement angles that must occur on a varying long-bone shaft. Still, the frustrations in defining the mechanism and limitation of a bioelectric phenomenon in bone did not stop investigators from speculating about its physiologic application and clinical use.

If mechanical energy is converted to electrical potential in living systems, a wide range of effects may be produced. "Theoretically, these include control of cell nutrition, local pH control and enzyme activation or suppression, orientation of intra- and extracellular macromolecules, migratory and proliferative activity of cells, synthetic capacity and specialized function of cells, contractibility and permeability of cell membranes and energy transfer."[17] Bassett published a review paper in which he speculated about the mechanism of these diverse biologic functions.[17] As an orthopedic surgeon, he focused upon the bioelectric nature of bone. Bassett and Becker[8,10,18,19] hypothesized that certain aspects of bone growth were under electrical control. Bassett felt that "changes in the orientation and mass of bone are controlled by stress-generated electric potentials. . . . Bone may function as an exquisitely sensitive piezoelectric gauge, responding to a slight jar or deformation."[9] Using this line of reasoning, Jahn stated, "When an electrical potential is applied to almost any biological structure, the migration of ions is the most rapid and obvious effect to be expected. . . . It might be possible to increase bone growth by means of slowly alternating electrical potentials similar in magnitude and frequency to the naturally occurring deformation potentials in an active animal."[20]

There have been many experiments to utilize measured electrical output as controlled input in an attempt to grow bone selectively. Basically these experiments consisted of implantation of low voltage, low amperage D.C. power sources electrodes applied on, in or adjacent to viable bone. The results of such experiments were confusing and often contradictory. For example, Bassett, Pawluk and Becker[18] were able to induce substantial bone growth around implanted cathodes. O'Connor *et al.*[21] repeated this work but their results showed that the positive terminal produced more osteogenic activity than the negative terminal implanted in dog femora. Heinrich[22] induced osseous calluses but felt that they could be equally attributable to the surgical trauma or the electrical effects of his implanted electrodes. Friedenberg *et al.*[23] applied between 5 and 20 microamperes of current across distal epiphyses of rabbit femora; they found a direct relationship between the current range and osteoblastic activity. The cathodal new bone formation was both osteoblastic and metaplastic, while the small amount of new bone found at the anode was metaplastic. Minkin *et al.*[24] attempted a similar experiment on the distal epiphyses of rabbit femora. They also concluded that "direct current may cause increases in bone growth, but . . . it differs little from that caused by the implantation of a foreign body (i.e., dead stimulator)."[25] None of these investigators considered the optimal current density (amperes/unit area) exposure in their experiments.

In 1967 Becker and Murray[26] proposed that there was "trigger stimulus" or threshold that initiated a sequence of cellular events. There appeared to be

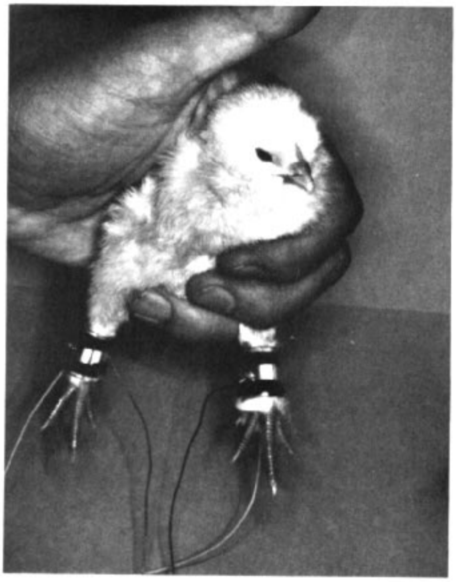

Fig. 1 Chicken with insulated cast/electrode device on legs which delivers a high voltage electric field across a growing long bone from a D.C. power source.

an optimal range and distinct limit to this stimulation. These investigators and others have tried to find the margins of this limit. It has been found that the current may be applied directly[18,23] or induced indirectly[27,28,29] but must be D.C. rather than A.C. (Fig. 1). The current range (not density) may vary from 1μA to as high as 20μA to produce bone repair or bone growth effects. Osteogenic electrical energy is likely to be a unidirectional signal, otherwise it might mediate both apposition and resorption alternately, yielding a net lack of effect. The accompanying voltage levels must also be kept low or within the 1 to 7 mv range. Apparently oscillation of the applied current and voltage enhance the bone growth response up to approximately 100Hz[30,31] with the ideal being at 1 to 50Hz. In summary the inducement of bone growth or partial multitissue regenerative growth is related to current density and an extremely low power and oscillation level.[26,32] The manipulation of the current density value may be the critical factor in producing initial morphological changes in "repair cells"[32] and alteration of bone surface.[29]

Regeneration Versus Repair

There are two related areas of active investigation which utilize the principles discussed above. The first is concerned with the natural regenerative process. When a living organism is injured, an electrical potential can be measured at the site of injury. This is a voltage difference or "wound-healing potential" which emanates from the release of amines and other biochemical molecules.[33,34] If this potential is measured in two closely related species, one of which can regenerate a limb and one of which can not, the voltages will be different. The method for all nerve impulse propagation is the transfer of electrical energy along the nerve axis. Damaged or amputated nerve tissue produces the greatest amount of electrical potential at the site of injury. Singer observed a direct relationship between the degree of nervous system unity of the limb and the ability of the animal to regenerate an amputated extremity.[35] Therefore, he reasoned that the regenerative ability in lower animals may be due to a high ratio of nerve supply to the cross-sectional area of an amputated stump. Singer then surgically increased the nerve supply to an amputation site and produced crude regeneration of limbs in a nonregenerating species. The ratio of peripheral nerve tissue to extremity tissue is very low in higher mammals, thus it is unlikely that this neurosurgical technique could be used to restore human extremities. Workers that followed him made the observation that perhaps the important factor in the regenerative process is not nerve tissue but electrical growth stimulation. Becker feels that the regenerative ability and interrupted nerve transmission is a "primitive data

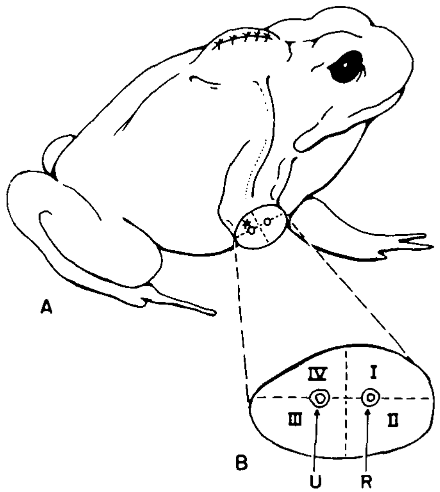

Fig. 2 A. Adult frog with amputated forearm and electrode/power source sutured subcutaneously on the back of the animal. B. Cross section of forearm showing (R) radius and (U) ulna and four quadrants of critical bioelectric activity. (Courtesy of S. D. Smith)

transmission and control system that deals with such modalities as the receipt of pain sensations (indicative of an injury) and the control of subsequent repair processes (to insure that they were appropriate and adequate). . . . One reason why mammals can not achieve many kinds of regenerative growth is the absence of adequate electrical factors at the injury site."[36] By applying the critical theoretical current/voltage requirements at carefully selected anatomical sites in adult frogs after amputation, Smith[33,37,38] was able to cause adult frogs to regenerate primitive but complete limbs (Fig. 2). Becker modified Smith's devices and inserted them into the amputated forelimbs of young white rats. He observed a regrowth of organized bone, cartilage, muscle, nerve and vessels in most cases. "The amount and organizational patterns of the units formed far exceeded any growth naturally seen or previously obtained by any technique."[36] The clinical implications of these experimental procedures is not the regeneration of human limbs, but the possibility of control of differential tissue growth to produce more restorative healing. For example, low level electric currents can cause differentiation and stimulation of a cell population[26] and differential regrowth of multiple anatomical systems.[33,36] The neural influence upon bone growth has been observed in the deformities associated with poliomyelitis. Researchers have performed experiments to assess the degree, direction and extent of morbidity associated with denervation or interruption of neural impulse transmission in growing animals. Drachman *et al.*[39,40] produced "club foot" in newborn chicks through the infusion of curare into their fetal circulatory system which hindered prenatal peripheral nerve transmission. Moss and Salentijn[41] presented data to show that growth patterns are influenced by neural developmental pathways. The *norma lateralis* growth of the mandible ascribed by the three inferior alveolar nerve foramina appeared to follow the same logarithmic growth curve as the course of the inferior alveolar nerve. Unfortunately, it is not clear what the growth pattern and extent would be in the case of very early denervation. The possibility of restored growth direction and tissue differentiation via selective bioelectrical direction is fascinating.

The second type of research, bone repair, has even greater application. The two research areas are intimately related, since normal fracture healing does not form scar tissue and is the only natural regenerative growth process seen in the mammal. When bone is fractured, the measurable electrical activity is quite different from that seen in mechanical stress. A positively charged dipole appears at the opposing fracture ends for several hours.[42] This means that a nonuniform positive electric field radiates from the fracture site. This field attracts "repair molecules" such as proline and glycine, the basic amino acid building blocks for collagen, which are negatively charged at a neutral pH. These molecules rapidly migrate in an oriented electric field.[29] They have recently been shown to congregate in areas of preferential bone growth in organ culture[28] and *in vivo*[29] by radioautographic techniques. Directly adjacent to the positive dipoles are areas of negative potential. These cathodes actively repel local oxygen. Low local tissue oxygen tension is a favorable environment for new bone and cartilage growth[43] while hyperoxia initiates bone resorption.[44] Finally, the low tissue pO_2 activates mitochondrial release of calcium which, in turn, may become the "seed" to initiate the local calcification process.[45]

The new osteogenesis or remodeling at a periosteal surface proceeds differently. Electrically active "repair" response apparently operates according to Wolff's law. Bone contains oriented fibers of collagen which, if stressed, generate negative electric potential toward the side of the applied stress. This electrical imbalance creates a minicircuit. The accompanying electrical field vectors orient tropocollagen and ultimately collagen in a direction which resists the lines of stress. This matrix supports osteogenesis. The resulting new bone is formed on the concave side and is oriented longitudinally and parallel to the force vectors. The electrical difference mobilizes needed components which gather at the site of injury; remodeling is a response to internal electrical vectors (signals) to rearrange and electrically neutralize the tissues already present.

The application of various types of electrical power sources to decrease fracture healing time in animals has met with success in many laboratories.[32,46] Limited and carefully controlled human clinical studies have been conducted to regulate healing of pseudoarthroses[47] and poorly healed fractures.[48] The results are promising and an interesting side effect is being explored. Fractures are often accompanied by difficult to treat pressure lesions such as decubitus ulcers. Low intensity direct current has produced a 350% increase in mean healing rate in ischemic skin ulcers in laboratory animals.[49] The electrically negative environment appears to be locally antibiotic because of a localized intense pH change, and upset in membrane potentials and permeability of the bacteria. This technique shows promise of becoming a new type of electrotherapy for infectious lesions that are resistant to normal antibiotic therapy.

Significance for Dentistry

The implications of the bioelectric phenomena in dentistry are many. Obviously the control of facial bone growth could be used to improve many growth anomalies, particularly bony deficiencies or reduce radical surgery morbidity. It is unlikely that this technique can be used to provide gross changes of mandibular or maxillary growth insufficiencies. It may, however, be feasible to grow bone in a cleft palate to afford a better surgical closure or improved alveolar contour. It might be used to enhance localized healing after complex surgical orthodontic procedures. The area of greatest promise is the restoration of periodontally diseased bone. Low current level, oscillating negative voltage is locally antibiotic and generates new apposition. Power sources can be applied in areas of root furcation involvement and infrabony pockets. Research is currently being conducted on a simple D.C. oscillatory mechanism that has shown promising osteogenic capabilities.[50]

Cochran,[51], Gillolly *et al.*[52] and more recently Zengo *et al.*[53] have examined the effect of mechanical stress on teeth and the resultant bioelectric potential generated in the alveolar bone. They have made it possible to directly measure the electrical potential generated from all forms of tooth movement at all levels of the alveolar bone. This method of study may become the fundamental model to investigate how various mechanical devices deliver their forces through the teeth to the bone. This should translate biomechanical theory into practice.

We now know that when we apply a force to a tooth we "bend" the alveolar bone.[54] The periodontal membrane transmits the tension of these forces to "bend" the bone opposite the side of active tooth movement.[55] This form of research may be used to determine if excessive pressure contributes to root resorption. If one uses excessive forces to push on bone, the deformation potential can exceed its limit and become zero. It is therefore conceivable that one could pass the deflection tolerance of alveolar bone and enter the range where the tooth starts to deform. This would establish the electrically positive environment which could initiate root resorption (Fig. 3). Thus root resorption may be secondary to a large force magnitude and direction sufficient to cause root distortion stimulating piezoelectric induced cementumclasia. "The threshold of resorbability between bone and cementum may lie in their relative susceptibility to piezoelectric induction."[56]

Two of the untoward sequelae of orthodontic extraction cases are the clefting of alveolar bone and the opening of the crown contact points at the closed extraction site. This often occurs in lower second premolar extraction cases, but can be seen at any extraction site.[57,58] Apparently parallel roots, lack of cumulated gingiva, and good occlusal interdigitation decrease but do not

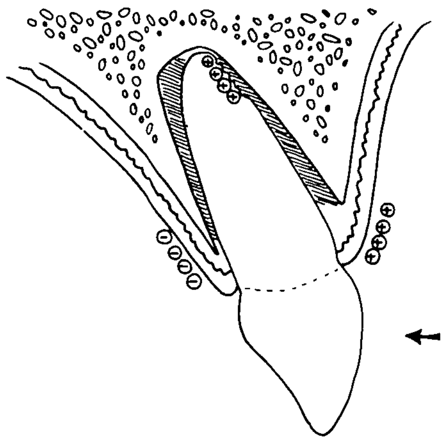

Fig. 3 Electrically positive charge appearing on the "deformed convex surface" of a tooth theoretically initiating root resorption.

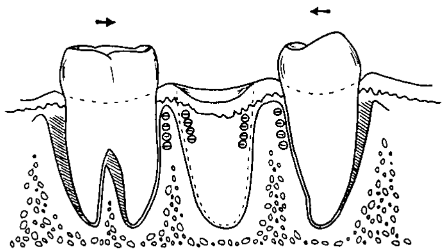

Fig. 4 Two negatively charged surfaces moving toward each other in rapidly moving tipped teeth.

prevent this phenomenon. The closure of an extraction site is a bone repair and remodeling process. The root movements of the mesial and distal teeth into the extraction sites are accompanied by varying degrees of tipping (depending upon the mechanotherapy used) and concave bending of bone. This means that two negatively charged bony surfaces move toward each other in rapidly moving teeth (Fig. 4). The like-charged opposing piezoelectric fields may interfere with bone cell nutrition and osteogenesis[59] producing a concentration of calcium ions and highly calcified tissue. The confluence of the like-charged surfaces may repel some of the organic matrix molecules. This could upset the normal bony architecture causing a disturbance in the buccal and lingual plate form. A radiopacity can often be seen at the bone of the closed extraction site. This density may be a thickened buccal and lingual plate. Thus, when bone is mechanically compressed by root paralleling mechanics, the "repaired bone" may act as a compressed spring and cause the local clinical relapse.

There is good evidence that the bioelectric effect is important in natural growth and development as it plays a role in remodeling. It may be the active principle behind Wolff's law. Bioelectric controls may be a more fundamental growth mechanism, however. Becker and his followers feel "that low level electrical currents and potentials . . . have the capability of bringing about very major biological effects of a very basic nature. The changes appear to be based upon perturbations produced in pre-existing biological electronic control systems which regulate very basic life functions. They hold significant promise for better understanding of life control systems and for clinical applications to certain diseases."[36] This brings us full cycle to Mr. Palmer and the question, what is life? We are seeing the reinvention and reapplication of an old idea, benefitting from the application of modern technology. The wisdom of philosophy often transcends science as perceived in a quote from the mystic Heschel, "The present is reunion with the past. But the future will be reunion with what is yet to be disclosed."[60]

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