Physical Factors in Bone Remodeling

Galileo first recognized the relationship between applied load and bone morphology. In 1683, he noted a direct correlation between body weight and bone size. During the next two centuries, others observed that bone remodels, but Julius Wolff, a German anatomist, was the first to link the two vital concepts. He noted that changes in bone mass accompanied changes in load, through the process of skeletal remodeling. In "The Law of Bone Transformation," published in 1892, Wolff explained: "Every change in the function of a bone is followed by certain definite changes in internal architecture and external conformation in accordance with mathematical laws." Stated more simply, *form follows function*. Although the mechanism by which bone cells transform mechanical or bioelectric signals into a useful biologic response is not fully understood, Wolff's observations are as valid today as they were nearly a century ago.

Bone Architecture

The architecture of the proximal femur beautifully illustrates the general principle that the external form and shape of bone *as an organ* and the internal organization of bone *as a tissue* are well adapted to the forces placed upon them. There are dynamic internal forces as well as static and dynamic external forces on bone. The internal forces are created by muscle contraction; the external forces, by Earth's ubiquitous gravitational field and by the dynamic compressive forces of weight bearing. The upper half of Plate 36 depicts the bony trabeculae of the proximal femur aligned along the lines of stress according to Wolff's law. This intersecting network of trabeculae is the biologic response to the sum of internal and external physical forces on that region of the skeleton. Both tensile and compressive trabeculae are present and correspond to the lines of force. Reduced weight bearing resulting from disuse or immobilization leads to a progressive thinning and eventual loss of trabeculae; those bearing the least weight are resorbed first. A similar pattern is seen in all weight-bearing bones, but the loss of trabeculae is most dramatic in the axial skeleton, especially in the vertebral bodies, which are largely made up of weight-bearing trabecular bone.

Mechanical forces also play a significant role in the external shape of bone. For example, the applied dynamic force of contraction of the gluteal muscles influences both the size and shape of the greater trochanter. If these muscles are paralyzed during skeletal development (as in certain types of poliomyelitis or in meningomyelocele), the greater trochanter does not attain its normal size and shape

Bone Remodeling

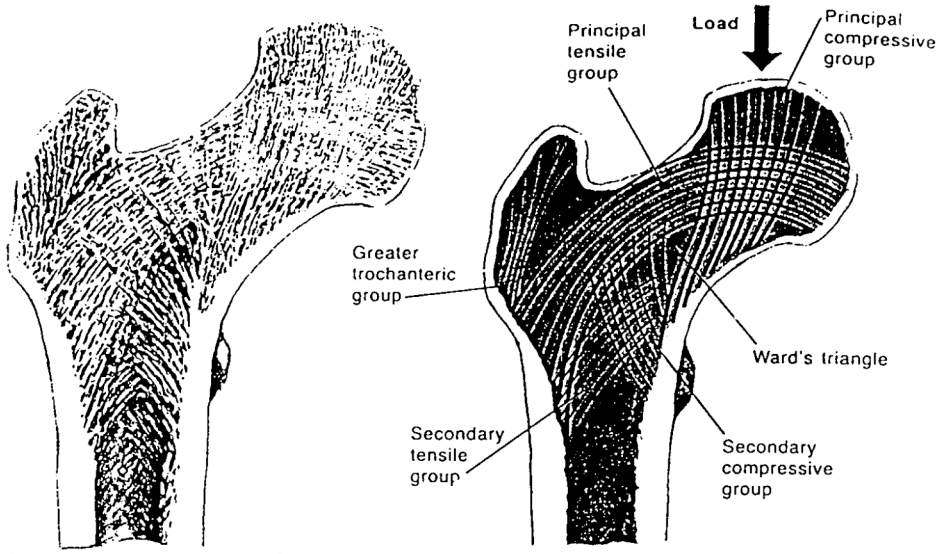
Wolff's law is also demonstrated by the straightening of a malunion of a long bone. With time, growth, and weight bearing, a malunion that has an angulation of as much as 30° will straighten completely, at least in the infant and young child (lower half of Plate 36). This phenomenon runs contrary to the laws of biomechanics, since continued weight bearing should cause an angulated structure to bend further until fatigue occurs. However, the exact opposite happens and the bone straightens with growth.

What is the explanation of this phenomenon? Some biologic or physical signal must arise from the concave side of the bone at the site of the malunion, inducing the osteoblasts there to lay down bone, and a corresponding signal must arise from the convex side of the malunion, stimulating the osteoclasts there to remove bone. What is the nature of this signal?

Four independent research teams began looking at this problem, each adopting the hypothesis that if an important function of bone is physical—namely, to bear load—then the signal that directs bone formation and resorption is perhaps a physical one. In the 1950s and early 1960s, Yasuda and Fukada, Bassett and Becker, and Shamos and Lavine carried out studies to discover the nature of signals in stressed bone. Also in the early 1960s, Friedenberg and Brighton began looking for signals in viable nonstressed bone. These studies determined that two types of electric signals (action potentials) are present in bone: *stress-generated*, or strain-related, potentials and *bioelectric*, or standing, potentials

Bone Architecture in Relation to Physical Stress

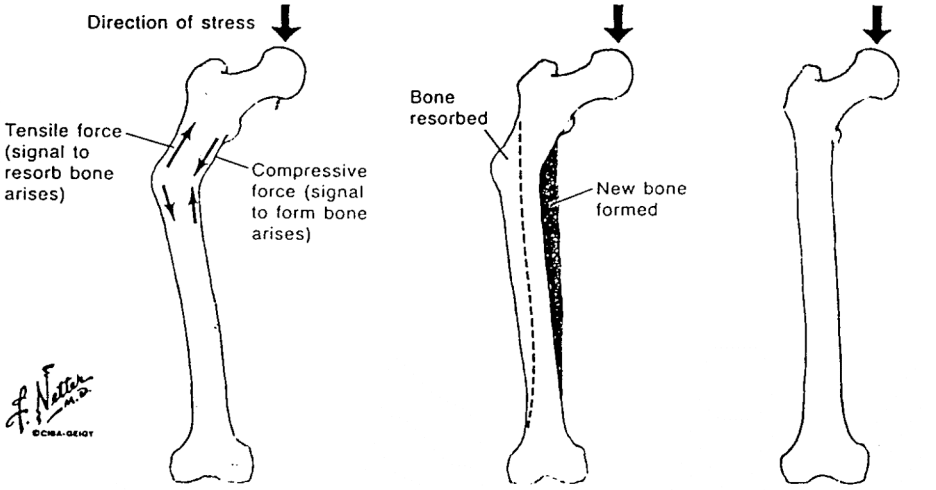
Wolff's law. Bony structures orient themselves in form and mass to best resist extrinsic forces (ie, form and mass follow function)



Trabecular configuration in proximal femur

Trabecular groups conform to lines of stress in weight bearing

Bone Remodeling in Response to Stress



Malunion of long bone, with angulation. During weight bearing, compressive force develops on concave side of bone, and tensile force develops on convex side

Compression signals osteoblasts to deposit bone on concave side, while tension signals osteoclasts to resorb bone on convex side

Bone thus remodeled to a form best suited for weight bearing. Although weight bearing might be expected to increase angulation, opposite occurs

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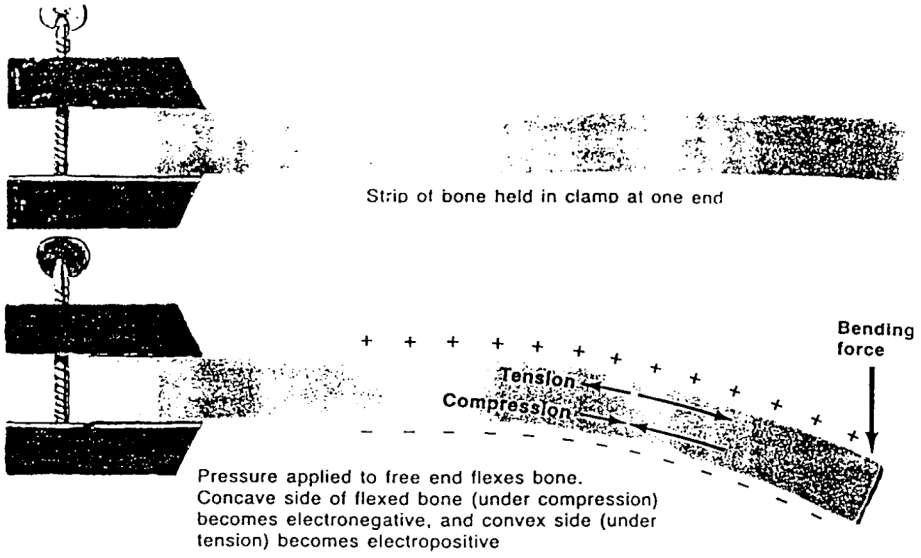
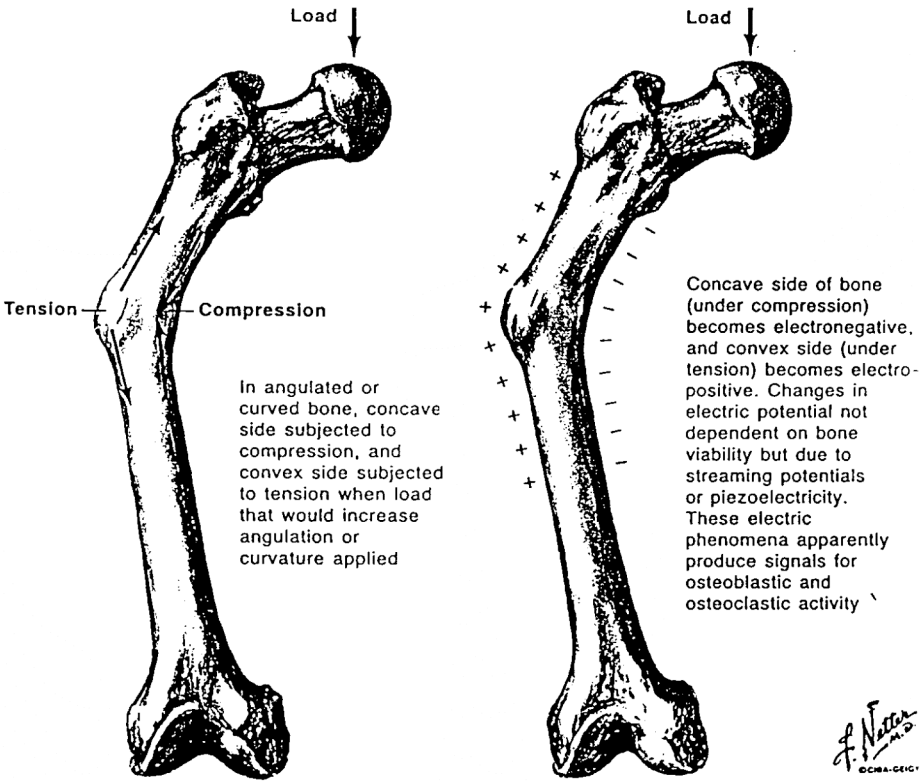


Pressure applied to free end flexes bone. Concave side of flexed bone (under compression) becomes electronegative, and convex side (under tension) becomes electropositive



Stress-Generated Electric Potentials in Bone

When bone is stressed, the concave side of the bone (the area under compression) becomes negatively charged, or electronegative, and the convex side of the bone (the area under tension) becomes positively charged, or electropositive (Plate 37). In the malunion of a long bone, the area of compression, where new bone will be formed, is electronegative, and the area under tension, where bone will be removed, is electropositive. These stress-generated potentials arise when the bone is stressed and are not dependent on cell viability. Research has also shown that the electric signal arises from the organic and not the mineral component of bone. Thus, stress-generated signals arise even if the bone is totally decalcified.

Bioelectric Potentials in Bone

Bioelectric potentials are measured from the surface of nonstressed bone (Plate 38). In the intact tibia, the growth plate–metaphyseal regions are electronegative, whereas the diaphyseal, or midshaft, region is not. When a fracture occurs in the diaphysis, the entire tibial surface becomes electronegative, with a large peak of electronegativity occurring over the fracture site and persisting until the fracture heals. A second peak of electronegativity occurs over the farthest growth plate. This latter finding is fascinating because a fractured extremity in a child frequently exhibits overgrowth not at the fracture site but in the growth plate near the end of the bone. The nature of the signal directing the growth plate to accelerate growth has never been identified, but the peak of electronegativity over the growth plate–metaphyseal area that accompanies a midshaft fracture may be such a signal.

To determine the source of action potentials in nonstressed bone, the following experiments were performed on a rabbit:

1. The vascular supply of the leg was interrupted, yet the electric potential over the proximal 7 cm of the tibia did not change. That is, the peak of electronegativity in the proximal tibia showed no significant change 30 minutes after ligation of the vessels.

2. The same result was found after the leg was denervated.

3. After injection of a cytotoxic drug (dinitrophenol), there was an immediate statistically significant drop in the electronegative potential. This suggested that the potential, which was measured from the surface of bone, was indeed linked to cell viability.

4. An in situ segment of the tibia was subjected to high-energy ultrasound waves, and a small segment of bone was killed. A corresponding statistically significant drop in the electric potential occurred over the nonviable region.

Potentials arising from nonstressed bone are called bioelectric potentials, meaning that they arise from living bone. Such potentials are dependent on cell viability and not on stress. Active areas of growth and repair are electronegative, and less active areas are electrically neutral or electropositive.

Studies have also shown that the application of small electric currents to bone stimulates osteogenesis at the site of the negative electrode (cathode).

Various in vitro and in vivo models have identified the processes and results of electrically induced osteogenesis. (1) Given the proper current and voltage, bone forms only in the vicinity of the cathode, whereas cell necrosis occurs around the anode when stainless steel electrodes are used. (2) Resistance rapidly increases between the electrodes, leading to a concomitant decrease in the current. (If a constant current is to be maintained, an active power supply using a transistorized control current circuit must be provided.)

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(3) Electrically induced osteogenesis exhibits a dose-response curve; a current of less than 5 μA delivered through a stainless steel cathode does not produce osteogenesis; a current of 5 to 20 μA produces progressively increasing degrees of bone formation; and a current greater than 20 μA induces bone formation that gives way to cellular necrosis. (4) Electricity can favorably influence fracture healing in laboratory animals, but for this to occur, the cathode must be placed directly in the fracture site. (5) With the proper current and voltage, electricity can induce bone formation in the absence of trauma and in areas of inactive bone formation, such as in the medullary canal of an adult animal. (6) The reaction at the cathode results in consumption of oxygen and production of hydroxyl radicals. (7) Pulsed direct current is not as effective as constant direct current in inducing osteogenesis. (8) The electrically active area of the cathode is at the insulation-bare wire junction and measures approximately 0.02 mm; therefore, when stainless steel is used as the cathode, the actual current density is 1×10^{-3} A/mm^2.

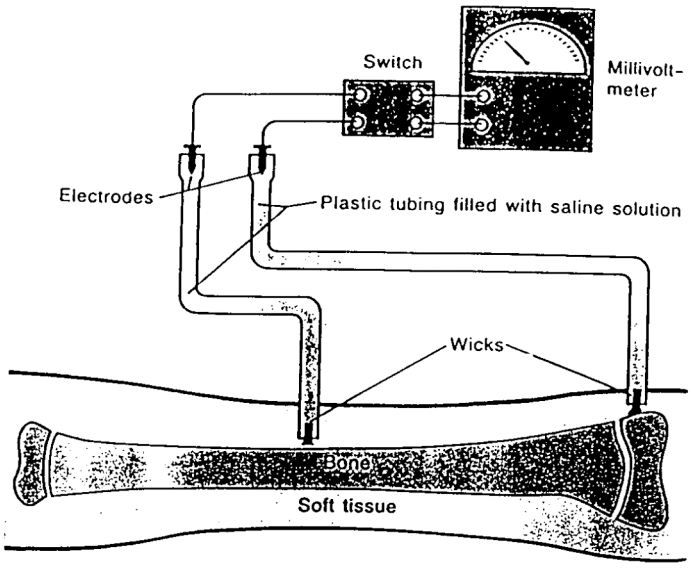
In addition, electricity can be induced in bone by means of an electric field with the electric apparatus remaining completely external to the limb. The electric field can be inductively or capacitively coupled to the bone. In inductive coupling, a current varying with time produces a time-varying magnetic field, which in turn induces a time-varying electric field.

In capacitive coupling, an electric field is induced in bone by an external capacitor (two charged metal plates are placed on either side of the limb and attached to a voltage source). Several studies have shown that both constant and pulsed capacitively coupled electric fields can favorably influence fracture repair in experimental rabbits and in the in vitro growth of the epiphyseal plate.

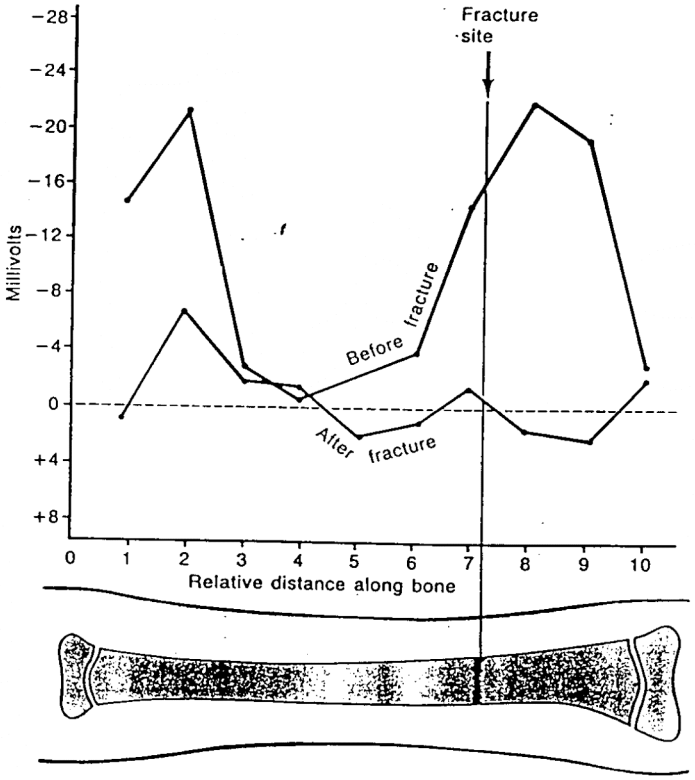
The mechanism by which electricity induces osteogenesis is unclear. It is known that the cathode consumes oxygen and produces hydroxyl radicals according to the equation $2H_2O + O_2 + 4e^- \rightarrow 4OH^-$. Thus, the oxygen tension (Po_2) is lowered in the local tissue, and pH is raised in the vicinity of the cathode. Studies have also shown that low Po_2 in tissue encourages bone formation: (1) low Po_2 has been measured at the bone-cartilage junction in the growth plate and in newly formed bone and cartilage in fracture calluses; (2) optimum in vitro bone growth occurs in a low-oxygen (5%) environment; and (3) cells of the growth plate cartilage, as well as bone cells, follow a predominantly anaerobic metabolic pathway. Howell and associates found that the pH in the growth plate at the calcification front was rather high (7.70 ± 0.05), suggesting that an alkaline environment is favorable to the mineralization of bone.

These local microenvironmental changes in the vicinity of the cathode lead indirectly to cellular changes that ultimately result in osteogenesis. Electricity may also act directly on bone and cartilage. Such a direct effect may be expected to activate the cell's cyclic adenosine monophosphate (cyclic AMP) system—activation of the intracellular, or second, messenger, which in turn activates various enzyme systems within the cell to bring about a specific physiologic response. Physical forces increase production of cyclic AMP at the site of new bone formation. If the cyclic AMP system is indeed activated by electricity, the electron or charge acts like a hormone in being the first messenger to bone or cartilage cells. Studies by Norton and associates support this hypothesis. They discovered a significant increase in cyclic AMP in epiphyseal cartilage cells that are subjected to an oscillating electric field. If this hypothesis is confirmed by further studies, the application of electricity in one or more of its forms may enable the orthopedic surgeon to modulate growth, maintenance, and repair of bone and cartilage. □

Bioelectric Potentials in Bone



Apparatus measures electric potentials from surface of in situ bone in rabbit. Differences in potentials present over length of bone in absence of stress. Potentials dependent on bone cell viability (eliminated by cytotoxic drugs and ultrasound, which kill bone cells). Potentials therefore referred to as bioelectric potentials



Ends of intact bone electronegative compared with midshaft When bone fractures, peak of electronegativity occurs at fracture site and persists until fracture heals. Second peak of electronegativity occurs at farthest growth plate. This may be significant with respect to overgrowth often seen in growth plate of fractured limb in children. However, signal to accelerate growth in growth plate has not been identified. These findings indicate that electronegativity occurs at sites of active bone growth or repair