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25. This article is based on the Third Annual Neuroscience Lecture, given in May 1983 at the Neurological Sciences Center, Good Samaritan Hospital and Medical Center, Portland, Oregon. The research was supported by grants from the National Science Foundation and the National Institute of Neurological and Communicative Disorders and Stroke.

RESEARCH ARTICLE

Endogenous Ionic Currents Traverse Intact and Damaged Bone

Richard B. Borgens

Abstract. *Living bone drives an electric current through itself and into sites of damage. Such "fracture currents" consist of two components: an intense, decaying current dependent on bone deformation and a stable, persistent current driven by a cellular battery. The latter is carried by chloride ions and, to a lesser extent, by sodium, magnesium, and calcium ions. Endogenous fracture currents are of the same polarity and similar magnitude as clinically applied currents that are successful in treating chronic nonunions in fractured bones. This suggests that the defect in biological nonunions may reside in the electrophysiology of repair.*

Bone is a structurally dynamic tissue. It modulates its shape in response to changes in load and can heal itself spontaneously. Bone is also electrically dynamic. Steady voltages have been reported along intact and damaged bone (*1*, *2*) and short-lived voltages have been measured in response to loading (*3*). It has been widely suggested that such electrical phenomena underlie the physiology of adaptive remodeling and repair, even though experimental evidence for this is scant. Most electrical measurements of bone have not been made under physiological conditions, and, to my knowledge, no measurements of endogenous electrical currents in living bone have been described. I report here my measurements of a steady ionic (electric) current traversing living bone at physiological temperature and the changes in current pattern and density induced by damage.

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Methodology

The ultrasensitive vibrating probe system precisely measures the density and direction of current traversing cells or tissues immersed in a natural medium. Essentials of its design and construction have been reported elsewhere (*4*), as has its use in a variety of biological studies (*5*). Current densities are routinely measured on the order of nanoamperes per square centimeter, with a spatial resolution of about 20 μm. The electrode is manipulated with a micromanipulator and viewing is performed with an inverted microscope.

Metatarsals of weanling mice were chosen as experimental material because they can be dissected from the digit intact, with little damage to the surface tissue ensheathments. The small size of the metatarsal (about 4 to 7 mm in length and 1 mm in diameter) makes it ideal for mapping with the vibrating electrode. Freshly dissected bones were immediately immersed in mammalian Ringer solution fortified with 5.5 m*M* glucose. Electrical recordings were usually begun within 2 to 3 minutes because of the necessary manipulations of the probe and specimen (Fig. 1). All bones were maintained at 37° ± 2°C, except where noted.

Intact Bone

Current flow was mapped in 64 undamaged bones. Current densities ranged from 0.5 to 12 μA/cm^2; the densest current entered the articular surface of the epiphyses while less dense current entered the remaining epiphyseal regions. The terminal cartilaginous regions of any bone showed current densities two- to sixfold larger than the diffuse current observed along the diaphysis. The latter current both entered and left the diaphysis, and no consistent pattern could be observed in this region.

Fracture Currents

Twenty-three of the 64 bones were also studied after being experimentally damaged. Ten of them were incompletely fractured with forceps (Fig. 1), and the balance were notched with a fine needle (the notch being 75 to 200 μm in width and penetrating the marrow cavity).

In two bones, the probe was placed in the fracture within 30 seconds after damage. Intense currents (129 and 102 μA/cm^2) were observed entering the lesion. In all other cases the electrical records were begun 2 to 3 minutes after damage. By this time, current densities had declined to 20.2 to 86.3 μA/cm^2. The decline reached an endpoint within 8 to 30 minutes after the injury (Fig. 2A). Plateau currents of 4.9 ± 0.5 μA/cm^2 (for all 23 bones) were exceptionally stable even after several hours (Fig. 2B).

Undamaged areas were mapped to determine whether any changes in outcurrent were associated with the increased densities of current entering the fractures. Foci of outcurrent were observed, but their position and pattern were high-

ly variable. Currents (5 to 10 $\mu A/cm^2$) were sometimes found leaving the bone directly adjacent to the fracture gap. Among 11 bones fractured to produce an angle, currents were found leaving the concave surface in five and incurrents were detected in this region in the balance. In some cases currents were measured leaving adjacent uninjured regions of the same face.

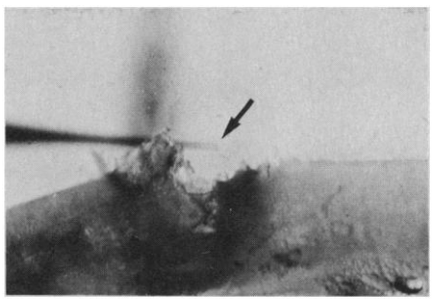

Fig. 1. Vibrating electrode (arrow) in a fracture gap in a weanling mouse metatarsal. The probe is visualized at the extremes of its excursion (about 30 μm) while vibrating at 460 Hz. The plane of vibration is perpendicular to the fracture gap to record the density and direction of current at this position.

Flexure Currents and Cellular Batteries

Four incompletely fractured bones were reflexed, and in three of them a current profile similar to that of the fresh fracture was observed: an intense current entering the fracture followed by a steady decline to a plateau of about 5 $\mu A/cm^2$. This suggests that the time-dependent current is associated with changes in the bone matrix and is independent of living cellular tissues.

Four bones were fixed by immersion in cacodylate-buffered (*p*H 7.2) glutaraldehyde for 48 hours and reequilibrated to mammalian Ringer solution for 5 days. The fixed bones were then fractured with forceps and explored with the vibrating probe in the standard medium at body temperature. In two bones enormous currents (484 and 970 $\mu A/cm^2$) were observed entering the fracture and in the other two smaller but still substantial incurrents (62.5 and 36.8 $\mu A/cm^2$) were measured. These currents declined to zero within 10 minutes. This demonstrates that the initial large incurrent is not associated with a living cellular battery.

Since investigations into the piezoelectric properties of hard tissue suggest collagen as a major source of transient, load-induced voltages (*6*), metatarsals were digested for 24 hours in collagenase (1.5 mg/ml). Large, swiftly declining currents were observed in four fresh fractures made in this digested bone. The current peaks (measured 2 to 3 minutes after lesioning) ranged from 16 to 23 $\mu A/cm^2$ (mean, 22.7 ± 4.0 $\mu A/cm^2$) and were similar to flexure currents measured in control bones left overnight in buffered Ringer solution without collagenase (30.3 ± 7.7 $\mu A/cm^2$; range, 12.8 to 42.6 $\mu A/cm^2$). Fractures were made in two bones demineralized in sodium citrate and formic acid, and in both cases a flexure current was measured entering the fracture. In glutaraldehyde-fixed bone, collagenase-digested bone, and demineralized bone, no plateau current was observed.

The metatarsal of the young mouse is still highly chondrified and can be sliced cleanly with a fresh scalpel, producing little deformation of bone substance. When 38 bones were cleanly transected with a scalpel, the steady component of incurrent (5.2 ± 0.38 $\mu A/cm^2$) was observed. Intense declining incurrents were not observed. A steady "injury current" was recorded in three separate bones for several minutes at 37°C, and the thermoelectric stage was switched to a cooling mode. As the temperature of the measurement medium fell (from 37° to 19°C), the current declined by 70 to 90 percent of its initial magnitude; this decline was reversible (Fig. 2C). Thus the plateau current is immediately dependent on ambient temperature and the flexure current is not. Glutaraldehyde-fixed bone was able to produce a flexure current at a temperature at which the plateau current is reduced or absent (Fig. 2D). These results strongly indicate that the injury current in living bone is of dual origin: an early and declining current initiated by deformation of bone and a steady current driven by a cellular battery. In fractures in nature both components exist simultaneously.

Cellular Source of the Plateau Current

The periosteum was tested as a possible source of the stable incurrents by scratching the surface of four bones with a fine needle under ×40 magnification. No significant current of injury was noted after such an operation. In two additional bones fractured in the central diaphysis a stable incurrent was measured (7.4 and 5.7 $\mu A/cm^2$). The entire ends of these bones were cut away, leaving only the center section containing the original fracture. Current was again measured entering this region and little change in its magnitude was detected (6.3 and 5.3 $\mu A/cm^2$, respectively). Thus cartilage (epiphyseal or articular) or periosteum is not the source of the plateau current.

When a notch was made in the bone with a fine needle, a stable current began to enter the notch as it was deepened toward the marrow cavity. This suggests that the bone of the diaphysis is the limiting resistance in the circuit and that the metabolically powered ionic pump is located in deeper investments—perhaps the endosteum or some other syncytium associated with the marrow cavity (*7*, *8*).

Table 1. Composition of the test media. All the media were prepared in double-distilled deionized water and buffered to *p*H 7.3 ± 0.1.

Medium	Concentration (m*M*)							Resistivity (ohms · cm)	Comment
	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	H_2PO_4	HCO_3		
Mammalian Ringer	149	2.7	1.4	0.49	144	0.36	11.9	80 to 100	
Na^+-free (tris)		2.7	1.4	0.49	144		11.9	130	Tris-HCl used as NaCl replacement, buffered with tris base
Na^+-free (choline)		2.7	1.4	0.49	144		11.9	140	Recrystallized choline chloride used as Na^+ substitute, tris buffered
K^+-free	152		1.4	0.49	144	0.36	11.9	100	
Ca^{2+}-free	149	2.7		0.49	141	0.36	11.9	78	
Mg^{2+}-free	149	2.7	1.4		143	0.36	11.9	78	
Cl^--free	149	2.7	1.4	0.49		0.36	11.9	200	All salts were gluconates

Ionic Dependence of the Currents

In studies of this type one can occasionally determine the ionic dependence of a current by making simple modifications to the standard bathing medium. Table 1 summarizes the various media used to determine the ionic dependence of the plateau current and Fig. 3 illustrates these effects.

When Na^+ was replaced with tris or choline chloride there was an increase in the leak current density. Initial current densities of 3 to 5 $\mu A/cm^2$ immediately increased by a factor of 1.5 to 8 in response to the removal of Na^+ (Fig. 3, A and B).

The minority cations (Ca^{2+}, K^+, and Mg^{2+}) were tested and little evidence supporting the active transport of K^+ by bone was found (Fig. 3C). A consistent increase in leak current density was observed in response to Mg^{2+}-free medium, and in two of four trials, a similar increase followed the removal of Ca^{2+} (Fig. 3, D and E).

Such increases in current density produced by the removal of cations can best be explained if the net current is the difference between cations pumped into bone and a larger movement of anions pumped in (*9*). Indeed, replacement of all the Cl^- in the medium with nontransportable anions (gluconates) produced an immediate reversal of current at the lesion (Fig. 3F).

A schematic model of these responses to ion replacement is presented in Fig. 4. Such an idealized model does not explain the sometimes enormous increases in current density occurring when choline is used as a replacement ion for Na^+, nor does it speak to the identity of other ions not tested in this study (H^+, HCO_3^-).

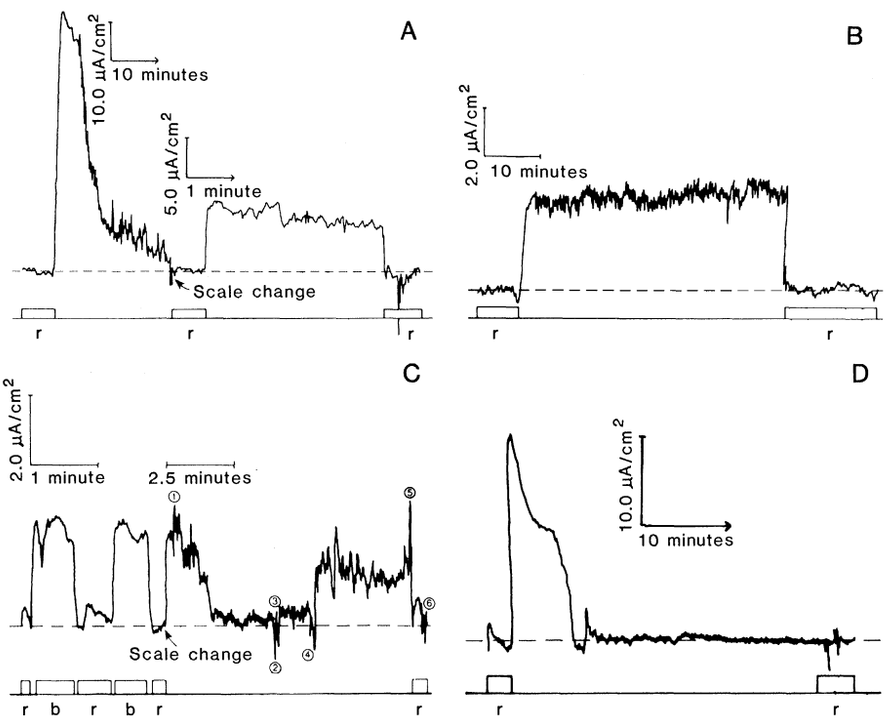

Fig. 2. Chart recordings of current density measured with the vibrating electrode. A reference (dashed line) was established with the electrode several centimeters from the specimen and out of the electrical field (r). The probe was then positioned in the fracture; deflections above the reference line indicate current entering the specimen; deflections below the line indicate current leaving. (A) Typical fracture current. The probe was placed in the fracture gap about 2½ minutes after the injury. Over 30 minutes the current declined steadily to about one-tenth the initial value. The probe was then moved to a reference position (a check for electrode drift) and brought back to the original measuring position. A sensitive scale and time base were chosen to record the steady component of the fracture current. The initial declining current is referred to as a flexure current. The steady component is referred to as the plateau current. (B) Plateau current 2.2 hours after the original injury. (C) Temperature dependence of a plateau current. Eighteen minutes after a notch was produced in the diaphysis a stable current was observed entering the fracture gap. The electrode was moved back and forth between the reference position (r) and the measuring position at the bone (b) twice to verify that the current was stable. At (1) the thermoelectric stage was switched to a cooling mode and an extended time base was used. In 3 minutes the current density had dropped nearly sevenfold and was oscillating abnormally. At (2) the temperature was 20.2°C. At (3) the thermoelectric stage was switched back to a heating mode. At (4) the temperature was 25°C. At (5) the current density had nearly recovered. A reference and temperature check was made at (6). The temperature of the medium was 38.3°C. Although the plateau current is temperature-dependent, flexure currents are not. (D) Flexure current in dead bone. This record was taken in a fracture 3½ minutes after damage was inflicted. The bone had been fixed in cacodylate-buffered 2.5 percent glutaraldehyde for 48 hours and reequilibrated with mammalian Ringer solution for 5 days before the experiment. The temperature of the measurement medium was 19.5°C. Note that the rapidly declining incurrent falls to zero and that there is no plateau current.

Discussion: Bioelectricity in Bone

Bone produces transient voltages in response to stress (*3, 10*). Steady voltages also exist along intact living bone and in or near fractures (*1, 2, 11*). These surface-detected voltages provide little quantitative data for physiologists; have, in some cases, not been measured under physiological conditions; and are subject to the technical difficulties encountered when surface contact electrodes are used to measure steady electrical potentials in biological material (*5*). Friedenberg and Brighton (*1*) found such "bioelectric potentials" to be negative in articular and epiphyseal regions and in the fracture site. These observations are supported by this study. This study does not support claims of a positive shift in injury potential at the fracture site (suggesting current leaving the injury), nor does it support claims of positive shift after periosteal injury (*2*). Injured muscle has also been suggested as being the source of fracture potentials (*11*). Since the metatarsals were free of muscle, it is clear that injured bone alone is fully capable of supporting large steady voltage gradients.

Transient changes in voltage have been ascribed to both piezoelectricity and streaming potentials (*3, 6, 12*). It is unquestioned that tendon, bone, collagen, and various other well-ordered biological materials exhibit piezoelectric properties in the dry state. However, recent experimentation greatly favors the streaming potential as the dominant mechanism underlying load-induced, short-lived potentials in physiologically wet bone (*12*). My experiments suggest that the flexure currents are independent of the crystalline components of bone or collagen, the most likely piezoelectric materials in hard tissue. Second, the current flow produced by the deformation of the fracture (independent of the cellular battery) declines over a period of up to 30 minutes. Such a long decay rules out a piezoelectric effect (since such voltages decay on the order of 1 μsec in body fluids) and suggests that a streaming potential underlies production of the flexure current (*12*). It should be noted that the character of flexure-generated

currents may differ between adult mammalian bone and cartilagenous immature bone (such as that used in these experiments) because of the substantial viscoelasticity of the latter.

It is widely accepted (without rigorous experimental support) that bone remodeling (Wolff's law) is dependent on load-induced voltages. Bioelectric measurements have suggested that the compression side of flexed bone is electronegative with respect to the tension side. Negative potentials during flexure are said to generate bone deposition and positive potentials are said to be responsible for bone resorption (*13*). This concept has also been applied to the adaptive remodeling that occurs after a fracture (*14*). The direct measurements of fracture current described in this article are not supportive of this thesis. The overall circuit about an injured bone can be exceptionally complex and variable—the only consistent observation is that current enters the lesion. Once current enters the bone substance, its pathway and density are entirely unknown. Bone is very porous, with many interconnecting canals and lacunae. The overall resistance to the flow of current would be inversely proportional to the extracellular space in these portals. Thus it is difficult to speculate on the magnitude of the fields associated with current flow. The electrical fields pertinent to biological activity would be those voltage gradients imposed on living cells along this current path.

Ionic Current and Bone Physiology

Bone is a difficult tissue for direct physiological measurements. Microelectrode (or ion-specific electrode) studies and tracer flux studies have largely been unreliable or unsuccessful (*15*). For example, shallow voltages (~4 mV) reported across the periosteum in tracer flux experiments are suspect, given their low magnitude and the indirect nature of their computation (*16*). However, bone extracellular fluid is different from body fluids in its ionic composition. For example, the concentration of K^+ is as much as five times higher in the extracellular fluid of bone than in serum (*15*). Curiously, there is little evidence for a "pump-leak" mechanism in bone to modify its interstitial environment. Purely structural evidence suggests that the ionic fluxes are largely passive. Although the periosteum and endosteum are sometimes described as epithelioid on the basis of their gross appearance and sometimes tight apposition, the lack of tight junctions suggests only a trivial barrier to the free diffusion of ions (*7, 15 17*). Osteocytes are connected to each other and to surface osteoblasts by tight junctions; however, these connections are spotty in their occurrence and it is doubtful if this possible syncytium can form an ionic seal between two fluid compartments (*7*).

Although these anatomical and physiological studies are unreconciled, direct measurements of charge movement in bone tissue offers strong evidence for an active pump-leak mechanism of ionic flux in bone. The vibrating probe does not register voltages in the extracellular fluid produced by diffusion gradients, and only registers voltage gradients on the basis of a current-resistance drop (*4*). The plateau current demonstrated here is almost certainly driven by an active cellular battery. This battery is dependent on temperature; is predictably modulated by changes in the ionic composition of the bathing medium (*18*); and is sensitive to Na^+, Cl^-, Ca^{2+}, and Mg^{2+}—further suggesting that these ions are transported across the "bone membrane." Furthermore, these experiments suggest that the membrane transporting ions between the extracellular fluid of bone and the extracellular fluid of the body is the endosteum or the saclike syncytium surrounding the marrow (*8*).

Fracture Currents and the Biology of Repair

It seems that endogenous currents are involved in bone repair, remodeling, and perhaps growth, rather than being just an epiphenomenon. Experiments in which tetracycline labeling is used as an index of bone formation indicate that areas of steady electronegativity in bone (current entering) are also sites of bone deposition (*19*). Also, artificially applied weak

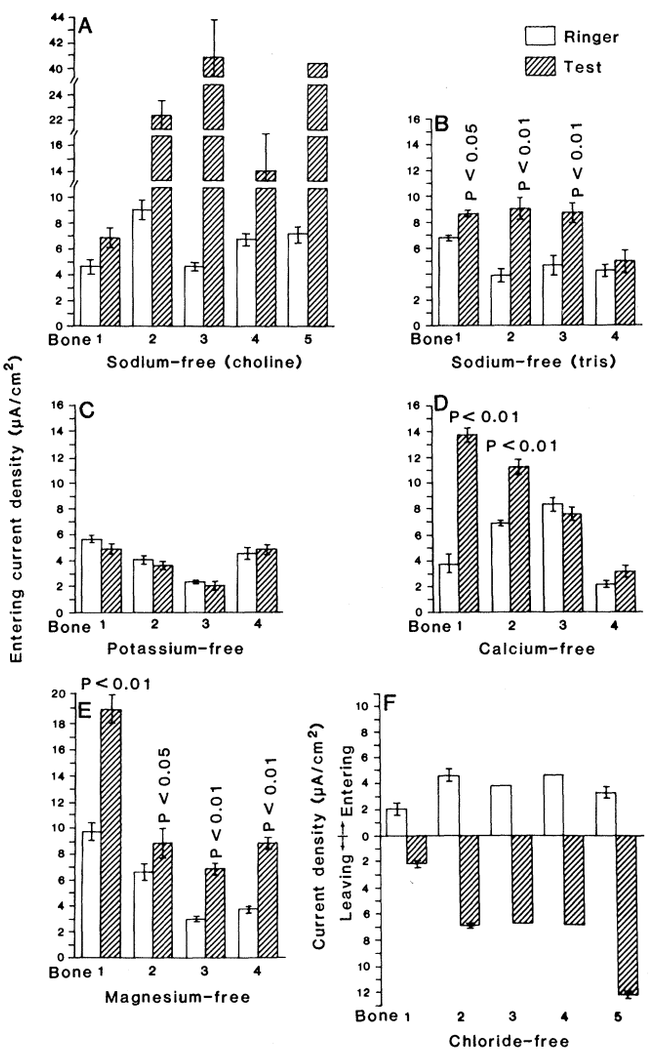

Fig. 3. Steady current in fractures in response to changes in the ionic composition of the bathing medium (see Table 1). Four to six separate recordings of a peak and stable current entering the severed bone were first made in Ringer solution. The bone was then washed twice in test medium and another set of measurements was made in that medium. Values are means ± standard errors for each set of these measurements. No error bars are depicted where the multiple recordings were identical. In (A), choline chloride (recrystallized) was substituted for NaCl and the medium was buffered with tris. Note the sometimes enormous increase in current density recorded after this replacement. In (B), more modest increases were observed when Na^+ was replaced by tris. In (C), no effect was noted after changing to K^+-free medium. In (D), a lack of response to a Ca^{2+}-depleted medium is demonstrated in bones 3 and 4; however, a marked increase in current density is observed in bones 1 and 2. In (E), consistent increases in current density were recorded in response to the removal of Mg^{2+}. In (F), a complete reversal of the current's polarity occurred after immersion in chloride-free medium.

currents can heal clinical nonunions (*20*) and otherwise modulate bone resorption and deposition (*5, 14*). Do clinically applied d-c currents mimic the naturally produced currents in polarity and magnitude? It is necessary to implant negative electrodes in the fracture to achieve healing (*20, 21*); thus, extracellular current is pulled into the gap (*9*). The naturally produced fracture current enters the lesion as well. The area of ununited fractures in human long bones may exceed 1 cm^2. A four-electrode configuration (10 μA per electrode), as used clinically, would produce a density of 40 $\mu A/cm^2$ in a lesion of 1 cm^2—a value within the range of current densities naturally produced by fractures. These similarities suggest that a defect common to clinical nonunions may be in the generation of endogenous fracture currents.

If endogenous currents are essential to bone repair, they may provide a redundant control system. Since, in the animal, load is intermittently exerted on the lesion, intermittent flexure current may be a long-term feature of the electrophysiology of injury. For bones that receive little loading or deformation, the cellular battery will still pull current into the injury.

The idea that surface-detected injury potentials may help to control the response to damage is not restricted to bone, and this has been a fertile area of research since the mid-19th century (*5*). Our modern understanding of current flow in developing cells and tissues has largely rendered the surface detection of bioelectric potentials as an obsolete descriptive technique. However, one idea engendered by these antiquated measurements—that electrical phenomena may help to control the tissue response to injury—is undergoing a renaissance.

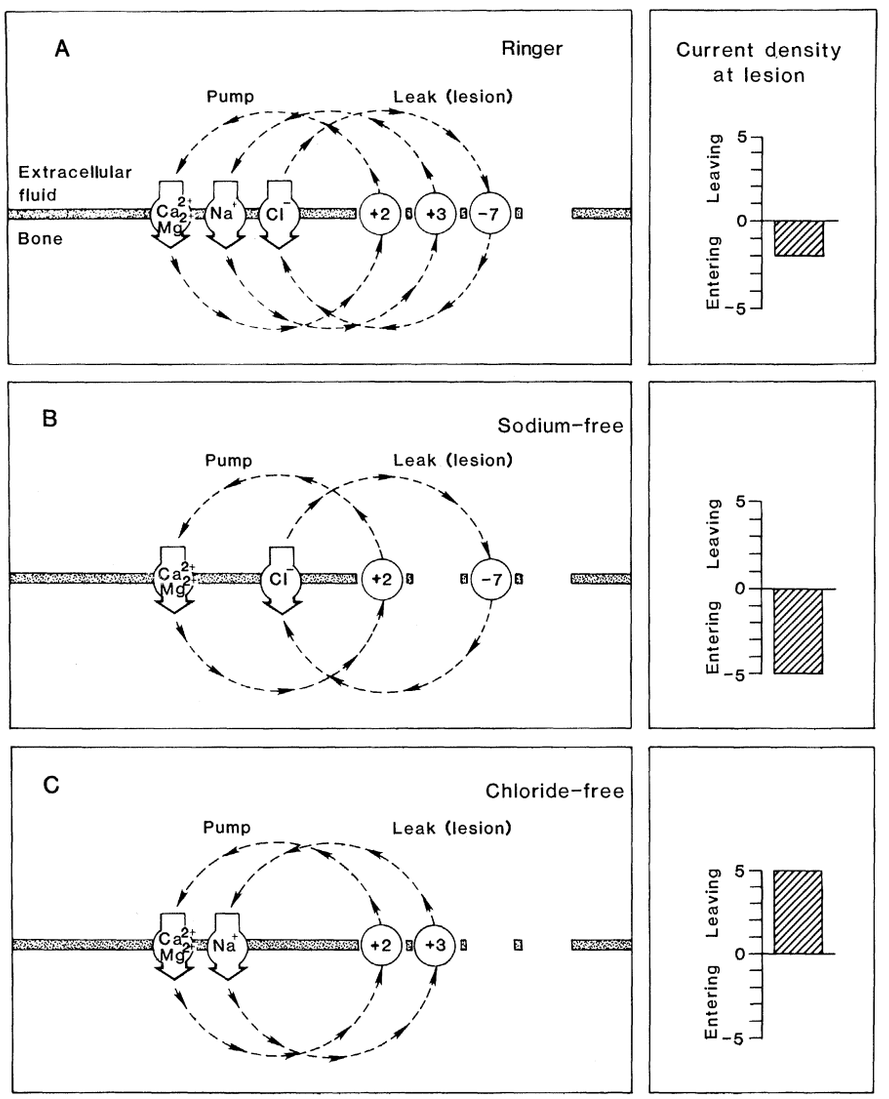

Fig. 4. Hypothetical pump-leak model for ionic current traversing bone. (A) Direction of extracellular current in Ringer solution and the actual direction (*9*) in which Na^+, Mg^{2+}, Ca^{2+}, and Cl^- are moved across the pumping membrane. All these components are arbitrarily assigned numbers at the leak site: negative values for current entering the lesion and positive values for current leaving it. Total current density calculated from these values is depicted in the bar graph at right. Note that in Ringer solution the net current flow is inward at the lesion because of a proportionately larger flux of Cl^-. (B) Effects of Na^+ removal. Note that magnitude of inward current flow at the leak is greatly increased. In a chloride-free medium (C) the direction of current flow at the lesion has reversed and the magnitude of the net density is larger than that measured in Ringer solution. This schematic is generally consistent with the response of current to changes in the ionic composition of the medium (Fig. 3).

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22. I thank M. M. Bever for expert assistance; L. F. Jaffe, J. W. Vanable, Jr., G. McGinnis, and D. Van Sickle for helpful discussions; and L. F. Jaffe, K. R. Robinson, J. W. Vanable, Jr., B. Hall, and A. Grodzinsky for reviewing the manuscript. This work was supported by PHS grant NS 19598-02, the Paralyzed Veterans of America, Research and Technology Foundation, and a Department of Defense contract (DA84C4012).

4 January 1984; accepted 6 June 1984