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The Symposium on Biodynamics Models and Their Applications took place in Dayton, Ohio, on 26-29 October 1970 under the sponsorship of the National Academy of Sciences - National Research Council, Committee on Hearing, Bioacoustics, and Biomechanics; the National Aeronautics and Space Administration; and the Aerospace Medical Research Laboratory, Aerospace Medical Division, United States Air Force. Most technical areas discussed included application of biodynamic models for the establishment of environmental exposure limits, models for interpretation of animal, dummy, and operational experiments, mechanical characterization of living tissue and isolated organs, models to describe man's response to impact, blast, and acoustic energy, and performance in biodynamic environments.

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THE EFFECTS OF HYPOGRAVIC AND HYPCODYNAMIC ENVIRONMENTS ON THE SKELETAL SYSTEM AND ACCELERATION TOLERANCE

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ABSTRACT

One of the rudimentary biomedical aspects of manned space flight, which remains to be investigated, is the long term influence of reduced gravitational forces, extended periods of physical confinement, and inactivity on man's musculoskeletal systems. Particularly, the relationship of altered bone strength to acceleration stress, such as may be encountered during space maneuvers, re-entry into the earth's gravitational environments, parachute opening shock, and ground or water landing impact.

It is common knowledge that the architecture of skeletal tissue is related to its function, of placing static and dynamic stresses on selective hard tissue components which in turn provide guidance in three dimensional space to cellular activity and direct skeletal architecture. The reduction of "normal" static and dynamic mechanical forces on the skeletal system removes or alters to an undetermined degree some of the stimuli controlling normal bone remodeling activity. The skeletal system responds to disuse (or better expressed altered use) by the dissolution of mineral and organic constituents, characterized by a decrease in bone mass while maintaining normal mineral composition. The mechanisms operative in producing these geometric and physiological alterations in calcified tissues, the control mechanisms, and time constants involved in these alterations, are not well understood. To produce a partial answer to the questions raised, adult rhesus monkeys were subjected to plaster of Paris cast immobilization for periods up to 240 days. Skeletal tissue was labelled at predetermined intervals. Following the immobilization period, these animals were exposed to longitudinal spinal impact in order to determine the threshold for mechanical damage to the vertebral column and changes in injury susceptibility as a function of immobilization time. These results seem to indicate that the observed differences in bone remodeling activity, skeletal architecture, as well as spinal impact tolerance, is described best not as an impairment of metabolic activity but rather as

a normal physiological adaptation of the skeletal system to the demands of the "new" environmental habitat. The time constant required by the system to lose over-abundant hard tissue and to stabilize in the new force environment is evident from these experiments. The implications of these animal experiments to future manned space flight and to man's acceleration tolerance is discussed.

INTRODUCTION

Demineralization of skeletal tissue has been shown to occur in men and animals while under the influence of reduced gravitational environments and hypodynamia. The triggering mechanisms for these radiographically and biochemically observed alterations in homeostatic behavior patterns is yet uncertain. However, there exists an ever increasing amount of experimental and clinical data indicating that bone remodeling activity will vary according to the degree of mechanical forces encountered for a particular environmental habitat and that the establishment, regulation, and control systems associated with mineral metabolism are at least in part, a function of a biological organisms mechanoreceptors responding to stimuli related to the gravitational forces of the earth ⁽¹⁻¹²⁾.

Future manned space flights, whether they be directed to manned space stations, journeys to the lunar proving ground, or exploration of the nearby planets, will require flight crews to remain in the confined environments of space vehicles and space stations, and to be exposed to the hypodynamic environment for extended periods of time.

One of the rudimentary biomedical aspects of manned space flight, which remains to be investigated, is the influence of reduced gravitational forces, and extended periods of physical confinement and inactivity on man's skeletal system and its relationship to mechanical stress, encountered during space maneuvers, as well as the final phases of space flight such as re-entry into the earth's gravitational environment, parachute opening shock, and ground or water landing impact.

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To produce a partial answer to the questions raised and their potential operational significance, osteoporotic rhesus monkeys were exposed to longitudinal spinal impact in order to determine the threshold for mechanical damage to the vertebral column, as well as to provide further insight into the time periods which constitute "skeletal adaptation" in terms of a "new" dynamic equilibria between reduced mechanical forces and the skeletal system.

EXPERIMENTAL METHODS

Selection of Primates

Forty-four, male, clinically screened, laboratory rhesus monkeys (*Macaca Mulatta*), ranging in weight from 13 to 15 pounds, were surveyed radiographically to demonstrate maturity by epiphyseal closure of the axial skeleton. The 22 control and 22 experimental animals were housed in an air-conditioned windowless room which was illuminated with fluorescent light. The animals were fed a standard diet of monkey chow. The control and experimental primates were placed in metabolic cages (which enabled urine and feces collection) for seven days. Baseline anteroposterior (AP) and lateral whole-body radiographs were taken of the entire skeletal system on day one of the conditioning period. The radiographic data taken during this period were used as baseline data. After seven days of conditioning, the control, as well as the experimental, monkeys were anesthetized with pentobarbital, 1 cc per 5 pounds, and again radiographed. The control animals were returned to the metabolic cages, and the animals selected for immobilization were prepared for being encased in plaster of Paris casts. Under anesthesia, the animals were wrapped in several layers of cotton gauze; the bony areas and prominences were padded with felt. Quick-setting plaster of Paris was added to construct a full-body cast (Figure 1). The experimental animals were hand-fed (required by the arm immobilization) twice daily; food intake was weighed and recorded. Monkey chow was dropped into the food trays of the controls. Water (distilled) was made available at regular intervals 16 times daily. At two-week intervals control and experimental primates were anesthetized, removed from their restraints, weighed, radiographed, and examined for complications.

Following the prescribed immobilization period, the immobilized and control animals were anesthetized and radiographed. Both primates were similarly restrained on the impact vehicle. The vehicle was raised to the predetermined drop height, released, and allowed to free-fall and decelerate. Immediately following impact exposure, the animals were killed with an overdose of pentobarbital. The entire vertebral column was grossly dissected. Macrophotographs were taken and analyzed in detail for evidence of atrophy. Samples from specific regions of the controls were compared with corresponding regions of the immobilized bone. Radiographs taken in vivo and following necropsy were studied to compare trabecular architecture patterns.

Processing of Material

Bones selected for the study were dissected and stripped of all soft tissue. Sagittal and transverse plane segmental sections were prepared using a machinist's circular saw. The trabecular structure and marrow cavity were stripped of haematopoietic and fatty tissue with a high velocity stream of water. Cortical bone was defleshed by hand picking and masceration. The specimens were identified, blotted, and dried in air.

In order to determine the threshold for mechanical damage to the vertebral column, a study was initiated which established the vertebral body compression fracture levels for the normal adult rhesus monkey. The Vertical Deceleration Tower at the Aerospace Medical Research Laboratory was modified to produce the desired acceleration time-histories. The impact vehicle shown in Figure 2 was constructed of glued and doweled laminated maple wood, reinforced with steel buttress plates. The support and restraint system within the shell of the carriage vehicle, although variable, (in terms of postural orientation), remained unchanged for these experiments. Nylon-reinforced cotton restraint straps provided standardized fixation of the primate torso. Tibial flailing was minimized by snugly restraining the lower third of both limbs to the supporting seat structure. Aluminum honeycomb was used as an energy absorbing brake. This hexagonal structure possesses the unique property

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Figure 1. Immobilized Monkeys

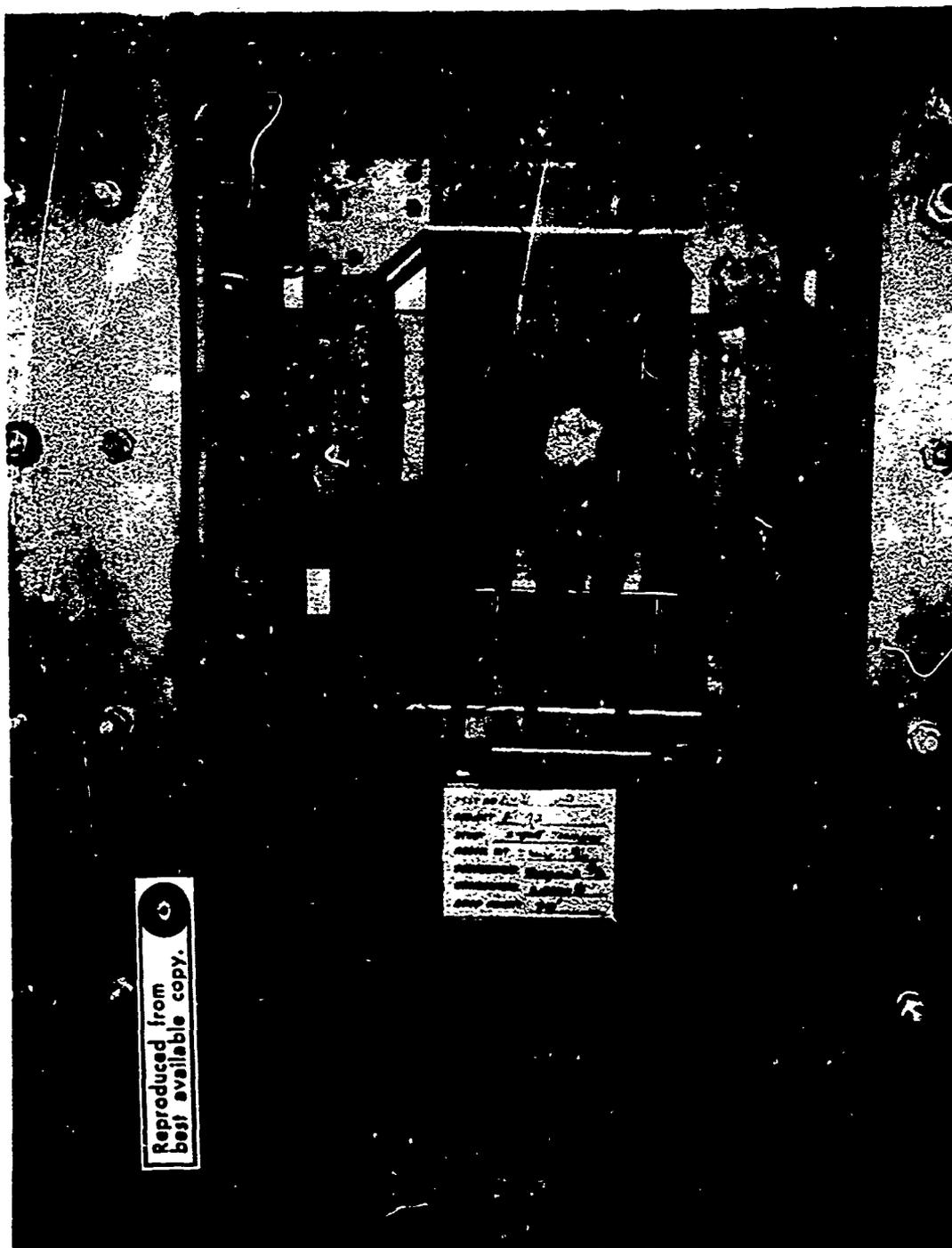


Figure 2. The Impact Vehicle with Experimental (Facing to the Front) and Control (Facing to the Rear) Animals

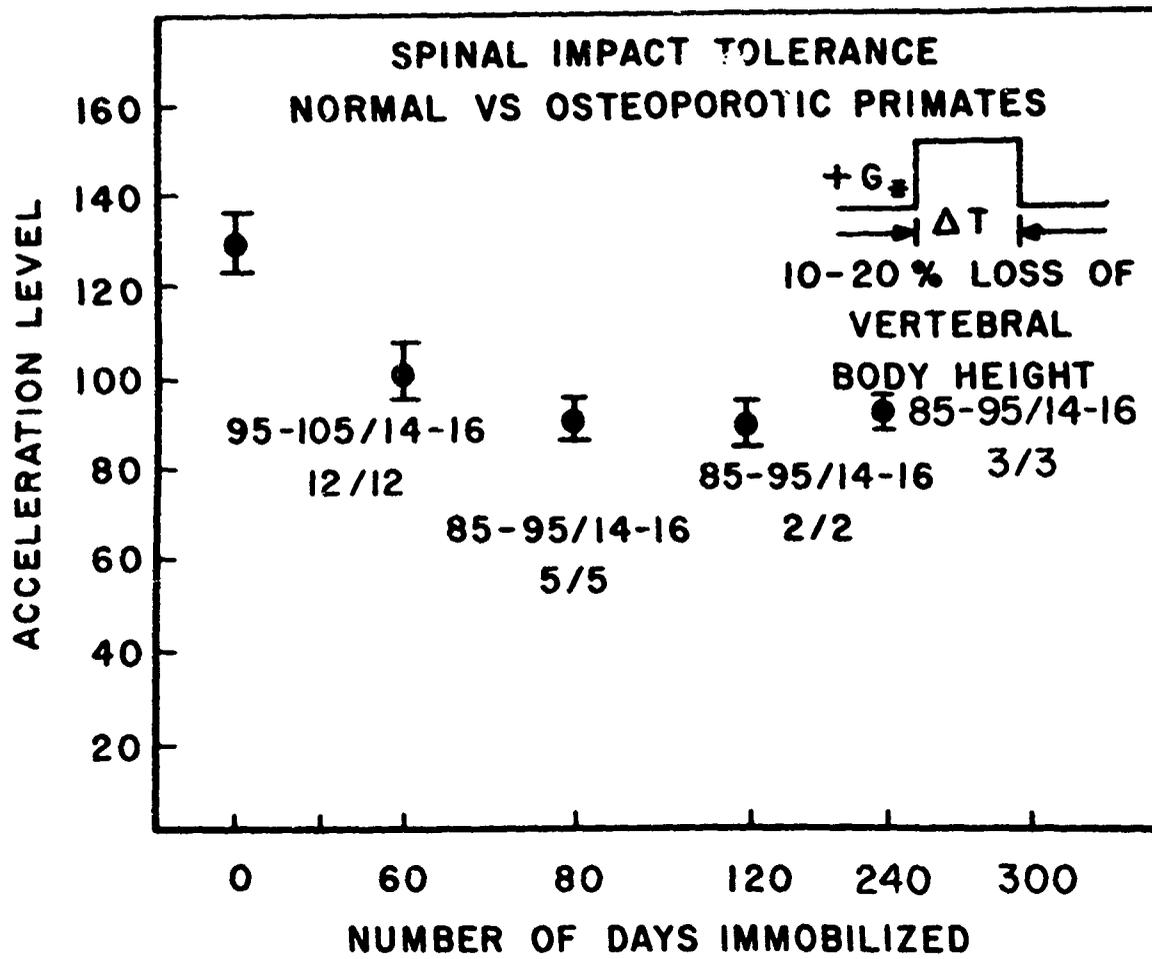


Figure 3. Spinal Impact Tolerance of the Normal and Osteoporotic Primates

of complete energy dissipation during constant load failure. Rectangular acceleration time-histories were selected because of their well-defined, practical, as well as theoretical, significance and interpretability. The magnitude and duration of the acceleration pulses were chosen so that they covered the most probable range of injury predicted from pilot experiments and presently available interspecies scaling data ⁽¹³⁾. The acceleration pattern was controlled by:

1. Drop Height
2. Aluminum Honeycomb Engineering Specifications
3. Total Surface Contact Area of the Impact Head.

Total time duration was essentially kept constant at 14 to 16 milliseconds. The acceleration level varied from 80 to 140 G's.

The acceleration inputs were in the $+G_z$ spinal direction. This body axis was selected because the injury mechanisms for this direction of loading are best understood and the results obtained seemed more likely to be more easily explained and incorporated into existing theoretical injury models of the vertebral column.

All primates were restrained in the impact vehicle in an upright position. The primates upper limbs were suspended in such a manner so that the weight of the arms was principally carried by the vehicle structure, thus, minimizing the total weight carried by the total spine, and minimizing anterior lip thoracic fractures of the vertebral body centrum.

Results

Upon completion of the prescribed immobilization period, the experimental animal was anesthetized, removed from its cast, and radiographed. The control animal was also anesthetized and radiographed. Both were restrained on the impact vehicle (one facing forward, the other facing to the rear) and exposed simultaneously to longitudinal spinal impact at the preselected acceleration time history.

The criteria for injury was a uniform decrease of thoracic vertebral body centrum height. Following impact exposure geometric radiograph measurements of traumatized thoracic vertebrae indicated that, following approximately 80 days of immobilization, spinal impact tolerance is reduced approximately 25 to 30 percent as shown in Figure 3. The range of the acceleration level is indicated by the first value, i. e. , for the case of 60 day immobilization, the animals were impacted at an acceleration level of 95 to 105g for a total time duration of 14 to 16 milliseconds. The total number of animals impacted was twelve and the number of animals which received 10 to 20 percent loss of vertebral height is twelve. As the number of days of immobilization increased, spinal impact tolerance decreased and began to plateau somewhere between 60 and 120 days where it essentially remained at this level for up to 240 days of immobilization and resulted in a total decrease in the relationship to normal spinal tolerance of 30 to 35 percent.

The experimental and control animals were immediately killed with an overdose of pentobarbital. A complete necropsy was performed and representative soft tissue samples of all organ systems prepared for histopathological examination. The entire vertebral column was grossly dissected as described earlier. For the immobilized animals, necropsy showed that the mechanism of energy dissipation within the vertebral bodies was to drive the viscous haematopoietic tissue out of the numerous paravertebral sinuses and beneath the surrounding ligamentous structures. The normal animals also showed a similar energy dissipation mechanism, however, less of the haematopoietic was qualitatively observed surrounding the vertebral column.

The entire axial skeleton was removed, grossly examined, defleshed, and macroscopically examined.

Macrographs were taken and analyzed in detail for evidence of hard tissue atrophy. Samples from specific regions of the controls were compared with corresponding regions of the immobilized bone. Serial radiographs taken in vivo, following necropsy and of dry specimens, were studied to compare trabecular architecture and cortical thickness.

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Radiographically, following approximately 60 days of immobilization, there is seen coarsening of the trabecular pattern at the distal and proximal ends of the long bones along with thinning of the cancellous bone within the vertebral body. Following approximately eight weeks of immobilization, macerated sagittal sections of vertebral bone compared to normal vertebral bone showed diminution in size and number of trabeculae, accompanied by a decrease in plate size, orientation, and porosity as well as reorientation of the trajectorial lines in cancellous bone. Macerated, vertebral cortical bone showed marked dilatation of bone marrow sinusoids and intraosseous channels (Figures 4 and 5). No gross disturbances were detected in the anatomic outline of the bones of interest. Sixty percent of the sagittal sections showed distinct paucity of spongiosa in the bony terminal end-plates.

Macroscopically, the most striking feature of macerated bone section is the quantitative and qualitative decrease of cancellous bone. The spongiosa of the osteoporotic vertebrae consists of a much more open network of delicate trabeculae. There is considerable atrophy of interconnecting trabeculae and a reduction or disappearance of bony plates (Figures 6 and 7). ©

The lamina terminalis, normally a well-defined redundant structure, is enforced by a compact layer of calcified material adjacent to the cartilaginous end-plate. The geometry of this structure is related to the function and metabolic state of the annulus fibrosus and nucleus pulposus. Following prolonged immobilization, these vertical trabeculae members enclosed within this structure are coarser, the marrow space larger and trabeculae more irregular.

One distinct type of structural bony failure was shown to be intervertebral disk prolapse (confirmed during necropsy examination) through the adjacent cartilaginous end-plate invoking the cancellous bone of the vertebral body centrum, followed by uniform crushing of the vertebral body centrum as shown in Figure 8 and reported earlier. Central cartilaginous end-plate tearing was not found during the necropsy of the control group.



Figure 4. Normal Lumbar-Vertebra (Cortical Bone)



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Figure 5. Osteoporotic Lumbar-Vertebra (Cortical Bone)

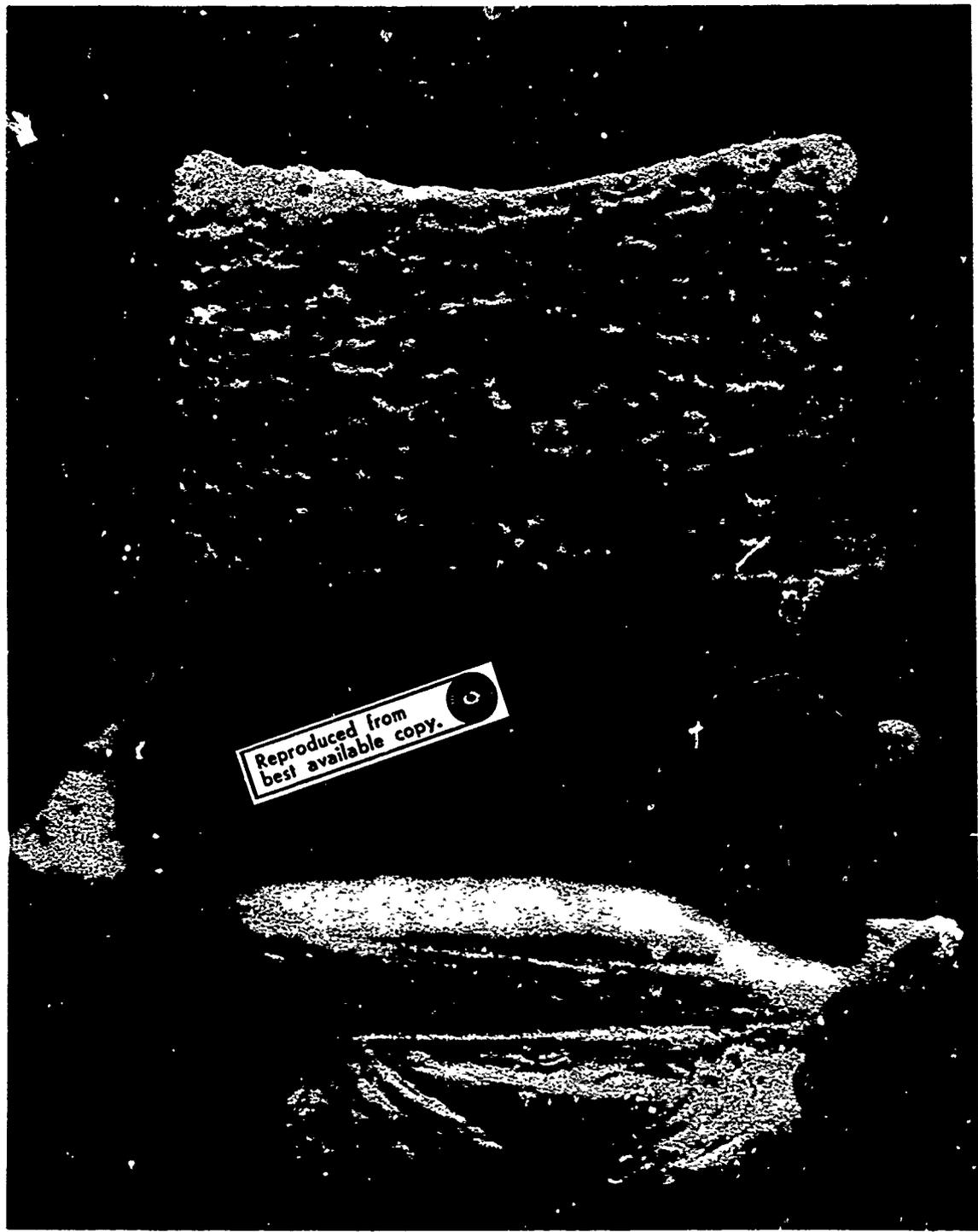


Figure 6. Normal Cancellous Bone (60 Days)

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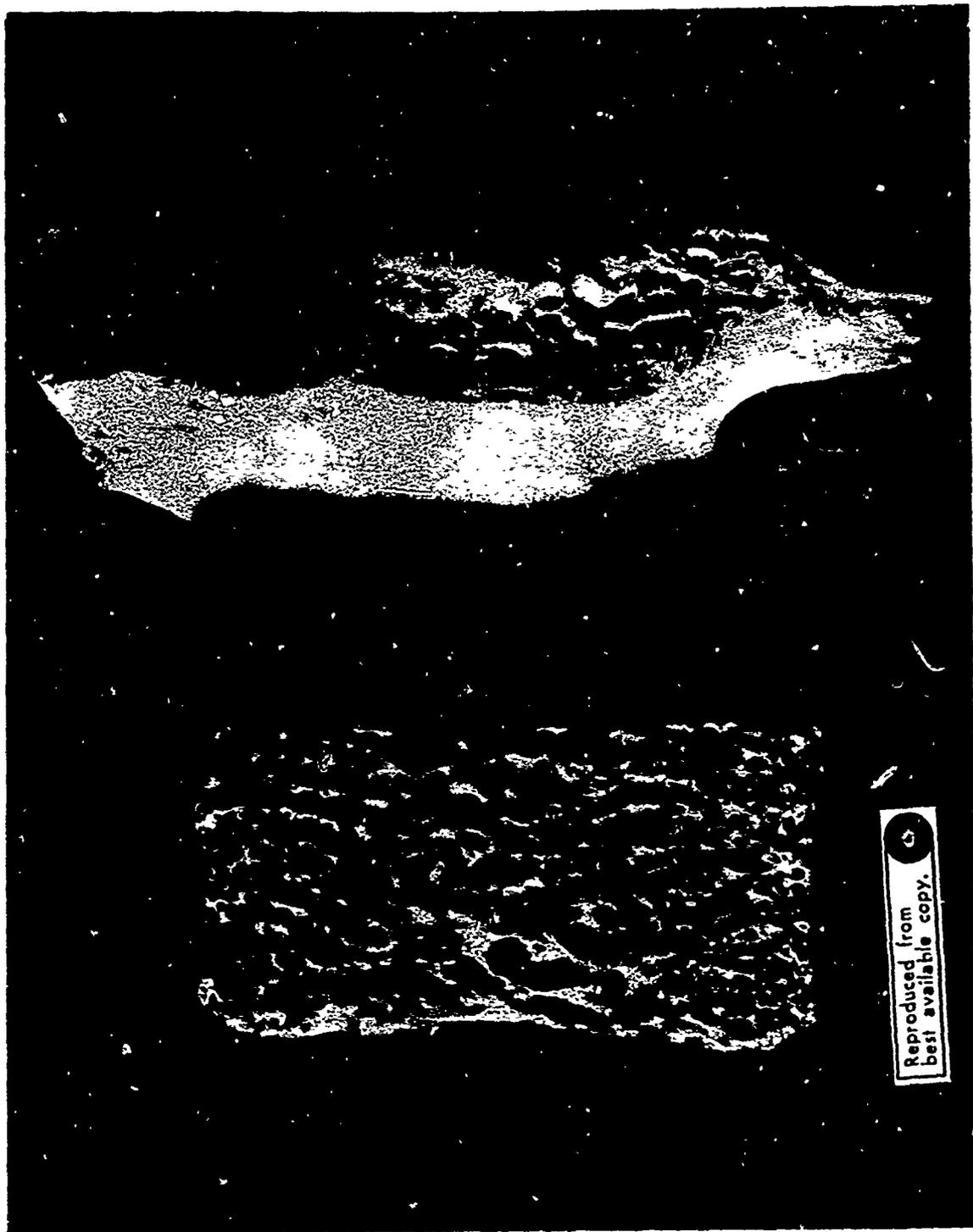


Figure 7. Osteoporotic Cancellous Bone (60 Days)

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Figure 8. Disk Prolapse Following Impact

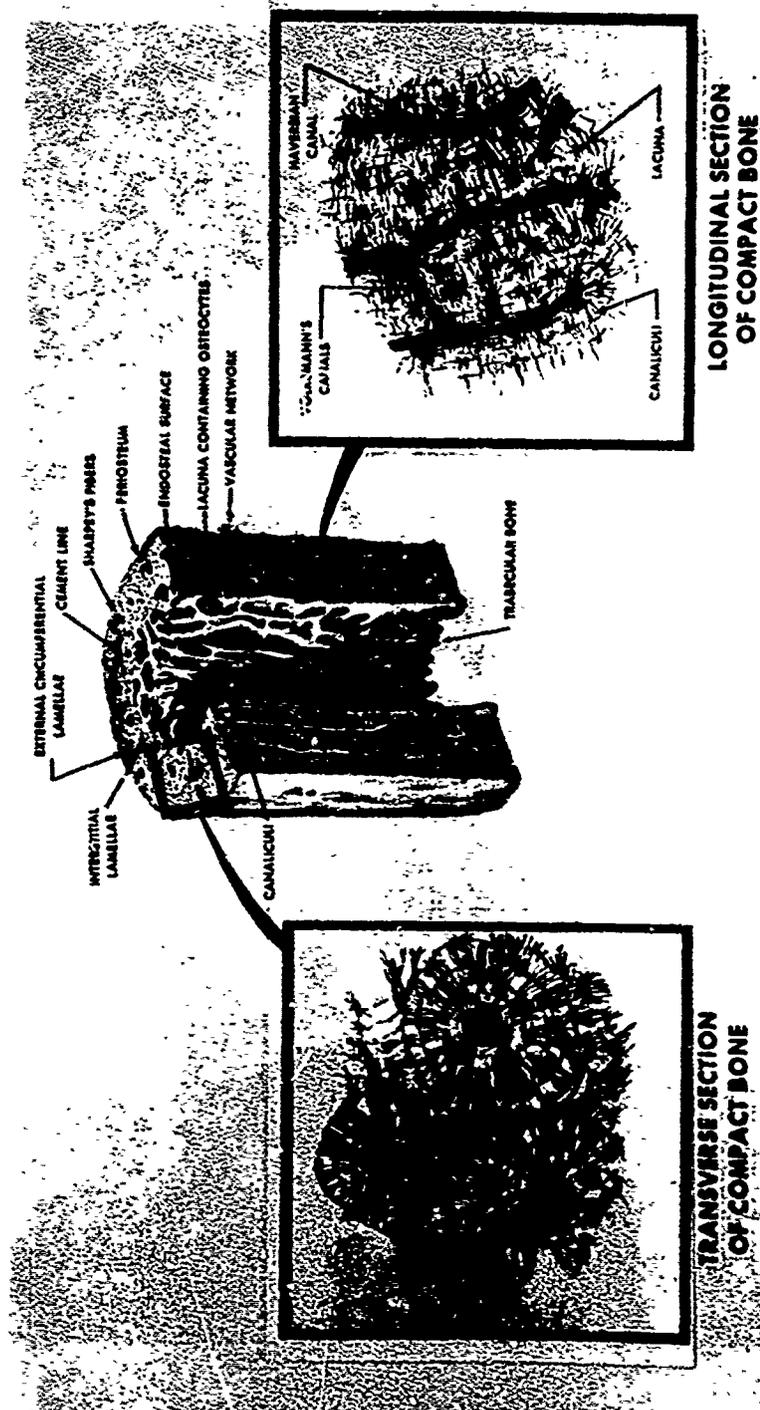


Figure 9. The Surfaces of Bone

Discussion of Results

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The influence of mechanical stress on the skeletal system has been well recognized. As early as Galileo, who derived mathematical relations between fracture resistance and bone geometry, investigators have studied the problem of the load carrying capacity of structural elements in the living system and the mathematical analysis of internal forces and deformations induced by applied loads.

The role of mechanical stress in forecasting bony architecture through influence on the cellular level has been a subject of long debate. The trajectorial theory of bone structure, as developed by von Meyer⁽¹⁴⁾, Bardeleben⁽¹⁵⁾, Roux⁽¹⁶⁾, and Wolff⁽¹⁷⁾, postulated that trabeculae were modeled along paths of compressive or tensile force. Wolff's classical statement was that, "Every change in the form and function of bones, or of their function alone, is followed by certain definite changes in their internal architecture and equally definite secondary alteration in their external configuration, in accordance with mathematical laws."

Koch⁽¹⁸⁾, in his paper, "Laws of Bone Architecture," concluded that cancellous and compact bone are so composed as to produce maximum strength with a minimum of material, and that in form and structure, bones are designed to resist compressive loads.

These concepts have been challenged by numerous investigators on the basis of such arguments that these analyses were based on two-dimensional stress analysis techniques for static conditions, assuming bone to be a homogenous material. However, two factors concerning the architecture of bone cannot be disputed: (1) that the structure of bones is related to the mechanical stress they are subjected to, and (2) there exists a relationship between bone architecture, the physical dynamics of remodeling, and between the geometry and cellular dynamics⁽¹⁹⁾.

When bone is subjected to normal, increased or decreased external forces, whether they be muscle pull, accelerations, or vibrations, its dynamic response characteristics depends not only on the magnitude of the external force and the

inherent strength of the bone, but also the manner in which the forces are applied externally and superimposed internally. The particular combination of forces, along with their rate and direction of application, will cause the bone to deform elastically (deformation without permanent set upon release of the stress), plastically (deformation in the inelastic or plastic range without fracture), or fracture.

Any variations in the magnitude, direction, as well as the rate of application of mechanical stress, will probably result in an alteration of the cellular dynamics of hard tissue, in terms of apposition, resorption (responsible for radiographic differences in bone volume), augmentation, and diminution (responsible for radiographic density changes) of both the mineral constituents and organic protein matrix.

Bone is a highly dynamic organ, anisotropic in organization, construction, and development; each elemental unit of this composite material is made by the deposition of successive layers of highly oriented collagen fibers which are subsequently mineralized. The normal mineralization process of bone requires two sets of factors:

1. an organic protein calcifiable matrix
2. concentration of calcium and phosphate ions in the extracellular fluid

and consists of two processes:

1. the formation of an organic protein matrix (principally protein, collagen, and mucopolysaccharides)
2. the deposition in this matrix of bone material is a complex microcrystalline compound of calcium and phosphate (hydroxyapatite), with a small amount of calcium carbonate.

The organization of the collagen fiber matrix and of the hydroxyapatite crystals is such that these two materials and probably a crystal "binder" all with different elastic moduli and strength, combine to form an optimal composite structure which accounts for the physical and mechanical properties of bone (20).

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Bone has been shown to be one of the most plastic organs in the body, able to adapt its architecture, its microscopic composition to chemical and mechanical stress, having a large metabolic turnover of mineral and organic materials and ceaseless chemical and physiological activity throughout life. As it takes part in unnumbered metabolic processes, its high remodeling rate reflects architectural changes, as well as reconstructive adaptations to abnormal functions to a degree surpassed by no other system in the body. The control mechanisms by which these processes are triggered is yet uncertain. It might achieve a state of cyclic relaxation oscillation; it might continually change its behavior or it might have a feedback system whereby deviations lead to a new dynamic equilibrium. Following the cessation of longitudinal growth, and throughout life, the cancellous and cortical bone of the skeletal system is replaced by the progressive resorption and formation of the organic protein matrix and inorganic bone salt at a characteristic rate with a characteristic variation which is a function of an undetermined number of physiological and ecological variables, which are in balance. Any changes in the net balance between the formation and resorption of bone play a critical role in such different phenomena as nucleation and crystal growth, chemistry of calcification, ion transfer between blood and bone, and absolute skeletal volume, and are probably a prerequisite to pathologic conditions.

The cells responsible for the specialization of hard tissue are the osteoblast, found in areas of active bone formation; the osteoclast, found in areas of bone resorption; and osteocyte, found in mature bone responsible for maintenance of normal blood-bone exchange. The precursors of these cells, characteristic of bone, are of mesenchymal origin and are acutely inter-related. During growth, mesenchymal cells frequently transform from one type of bone cell to another, yet are able to return the potencies common to the osteoclast and osteoblast. Little information is available concerning the feedback control systems responsible for the stimulation of the resting mesenchymal cell to activity, which results in the production of specialized cells; the osteoblasts and osteoclasts.

However, what is known is that the net balance between bone formation and bone resorption for a particular time period determines the bone remodeling rate, the architecture, as well as the mass of the skeletal system. The strength of hard tissue is dependent on the quantity of hard tissue per unit volume, the direction of loading, and the geometric configuration of the bone. If net bone resorption is greater than bone formation, a bony porosity develops, the physical and mechanical properties of bone decrease, and the structure becomes susceptible to deformation and fracture during normal weight bearing. If net bone formation is greater than bone resorption, osteosclerosis develops. (For instance, as observed in the changes of vertebral body structure in scoliosis.)

It is a common knowledge that the structure of bone mineral is intimately related to its metabolic activity and that the reduction of normal mechanical forces on the skeletal system removes some of the stimuli for normal bone remodeling activity. The skeletal system responds to disuse or immobilization by the dissolution and removal of organic matrix and inorganic material, characterized by a qualitative and quantitative decrease in bone mass yet with normal mineral composition [Geiser and Trueta ⁽²²⁾].

The etiology, clinical, and pathological features of disuse atrophy are by no means uniform, however, its manifestations are quite unvarying. These consist of a diminution in the size and number of trabeculae, accompanied by a decrease in plate size, orientation, and porosity. The thin bony plates of cancellous bone becomes progressively more fenestrated; are reduced to slender rods to be followed by the selective resorption of redundant transverse trabecular structures and the accentuation of primary trabecular trajectories. As the highly active cancellous bone is resorped, the burden of calcium homeostasis is systematically transferred to the endosteal surface of the skeletal system. Cortical bone is gradually cancellized, accompanied by the marked dilatation of bone marrow sinusoids and intraosseous channels.

In normal bones, osteons have been shown to develop first at the points of muscle attachment [Johnson ⁽²¹⁾]. Excessive muscle activity has been shown

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to accelerate the rate of osteonization. When bone is subject to mechanical stress with no muscular activity (as in the case of poliomyelitis), it is usually devoid of osteons, suggesting the osteonal architecture is not determined by genetics, but by the dynamic mechanical force imposed on bone by muscle pull. In disuse atrophy, the number of osteons in cortical bone decreases and the bone becomes a poorly differentiated structure.

In this study, the increased mineral metabolism and the loss of skeletal volume, along with the observed differences in skeletal architecture, seem to be due to a net loss of the over-abundant hard tissue and specialization or adaptation of the skeletal system to the demands of the "new" particular environmental habitat. However, this is not meant to imply that physiological disturbances and complications will not result from disuse of the biological system. On the contrary, the maintenance of "normal" homeostatic mechanisms of the body are effected by the interaction of numerous physiological systems. For instance, bedrest is an often prescribed non-specific therapy about which very little clinical information is known. Prolonged bedrest has been shown to result in a progressive loss of mineral secondary to bone resorption, increased urinary calcium concentration, and increased susceptibility to renal stone formation. Any alterations in the external environment or physical activity of an organism which produce biochemical or physiological stress, changes in temperature, electrolyte composition, hormone activity, electrical potentials, and Ph, will be counteracted by an unknown number of physiological feedback mechanisms within the organism in an attempt to reestablish the dynamic cellular equilibrium. This adaptative process involves quantitative changes in the control system, yet to be adequately described. It is speculated two types of adaptive changes may occur. One may be an extension of a zone of bone remodeling activity to another level (structural, physiological specialization). The second type results in an altered capacity to maintain an altered bone remodeling rate (general metabolic adaptation). Both types of changes extend the homeostatic mechanisms which eventually shift with time. As the limits of adaptation gradually become

narrower and impose severe limitations on the regulatory and control mechanisms, the end result may very be disturbed relationships in normal cellular dynamics and the possible factors in bone diseases. One other important factor which should be considered in skeletal cytodynamics is the chemical exchange of bone mineral. All bones are richly vascular, and permit the continuous exchange and flow of ions to and from the surfaces of the various holes in bone, namely the osteocyte lacunae, haversian canals, medullary spaces, canaliculae, primary longitudinal canals and volksinans canals (Figure 9).

Throughout life, there exists a continual transport process of ions from the various surfaces of bone which play an important role in the regulation and control of mineral levels in the circulating fluids. Without blood-bone exchange, it can be assumed that the circulation, diffusion impedance, and the exchange of ions within the skeletal system would become restricted; skeletal mineralization would take place, and eventually the skeletal system may become metabolically inert.

Since the skeletal system is "normally" an optimal architectural structure in terms of weight bearing, it would follow that the chemical pathways must parallel and remodel accordingly. The active homeostatic mechanisms in both circulating fluid and hard tissue must work continuously to maintain "normal" levels of circulating chemicals. If a particular mechanical environment constitutes a stressor and results in a prolonged physiological disturbance, the skeletal structure will equilibrate to the new chemical, as well as the functional environment; the end result will be a change of the mechanical and physical properties of the skeletal structure.

SUMMARY

The purpose of this study was to determine the effects of disuse atrophy of bone on spinal impact tolerance for the rhesus monkey. This study clearly demonstrates that disuse and inactivity has profound structural and functional effects on the weight bearing spine, in terms of decreased spinal impact tolerance.

The presently used biodynamic injury criteria for impact is based on laboratory experiments and field data, with adult human and animal subjects whose skeletal systems are assumed to be normal and healthy. Disuse atrophy decreases the overall mechanical strength of the skeletal system to such a degree that injury levels for acceleration exposure are significantly altered, for the immobilized rhesus monkey. There are indications that a similar analogy may hold true for man in space for extended periods of time. If this is true, new acceleration stress indices predictive of physiological conditions for the astronaut may become necessary. A considerably more detailed effort is required in order to thoroughly evaluate the consequences of the data reported in this study. Extreme caution must also be exercised to extrapolate quantitatively the time factors studied in this experimental series on the Macaca Mulatta to the human case. Bone remodeling dynamics among primates is probably similar, however, remodeling rates and their magnitude must be compared with reservation.

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