

BONE CHANGES SPACEFLIGHT AND BED REST FINDINGS COMPARED

SPACEFLIGHT

CALCIUM

URINE

INCREASE TO 300 mgm/d OVER 1ST 30 DAYS
STARTING DAY 1; THEN PLATEAUS AT
THIS LEVEL TO 84 DAYS
(BASELINE = 200 mgm/d)

* FECES

DECREASE OF 50 mgm/d OVER 1ST 10 DAYS;
THEN CONTINUOUS LINEAR INCREASE THROUGHOUT
FLIGHT DURATION (100 mgm/d ABOVE BASELINE
@ 25 DAYS; +200 @ 55 DAYS; +300 @ 84 DAYS)
(BASELINE = 600 mgm/d)

* SERUM

SLIGHT INCREASE (0.5 mgm %) WITHIN 1ST
5 DAYS; THEN PLATEAUS AT THIS LEVEL
(STILL WITHIN NORMAL RANGE OF 9-11 mgm %)

* BALANCE

INCREASING NEGATIVE BALANCE AS A FUNCTION OF
FLIGHT DURATION - EXPONENTIAL RISE WITH SLOWLY
DIMINISHING RATE OF RATE (-50 mgm/d @ 10 DAYS;
-200 @ 30 DAYS; -250 @ 60 DAYS; -325 @ 84 DAYS)

* HYDROXYPROLINE (URINARY)

INCREASE TO ABOUT 100 % OVER PREFLIGHT IN
1ST 30 DAYS; THEN SLOW DECREASE (75 % ABOVE
PREFLIGHT AT 84 DAYS)
(BASELINE = 45 mgm/d)

* BONE DENSITOMETRY
(OS CALAIS ONLY)

AVERAGE OF ABOUT 4 % LOSS AFTER 84 DAYS

* PROGNOSIS

LOSS OF 15 % BONE MINERAL AT 1 YEAR

BED REST

INCREASE TO 300 mgm/d OVER 1ST 30 DAYS
STARTING DAY 1; THEN VERY SLOWLY DECREASED
TO 250 AT 20 WEEKS
(BASELINE = 200 mgm/d)

NO CHANGE 1ST 2 WEEKS; THEN GRADUAL INCREASE
TO +100 mgm/d BY 5TH WEEK; THEN
PLATEAUS AT THIS LEVEL
(BASELINE = 600 mgm/d)

NO CHANGE

INCREASING NEGATIVE BALANCE TO -250 mgm/d
BY 1ST 5 WEEKS; THEN STAYS AT
THIS LEVEL

INCREASE TO 25 % ABOVE BASELINE IN
1ST 30 DAYS; THEN SLOW DECREASE
(12 % ABOVE BASELINE AT 12 WEEKS)
(BASELINE = 45 mgm/d)

AVERAGE OF ABOUT 10 % LOSS AFTER 12 WEEKS

LOSS OF 6 % BONE MINERAL AT 1 YEAR

* SIGNIFICANT DIFFERENCE BETWEEN SPACEFLIGHT AND BED REST

CESSATION OF BONE FORMATION DURING SPACE FLIGHT

Changes in calcium homeostasis present a potential problem for prolonged space flights. Calcium changes documented to date in humans during space flight include a decrease in bone mass and an increase in urinary calcium and hydroxyproline.

To investigate causes of the bone changes during space flight, we measured parameters of bone formation and resorption in tetracycline labeled rats which flew for 20 days aboard the Russian Cosmos 782 biosatellite.

The FIRST SLIDE shows the Cosmos spacecraft. About 20 hours prior to launch, rats were loaded in the craft in individual cages which were organized in blocks of 5. Each block of cages shared a common food and a common water source. The rats were fed 10 grams of a paste diet every 6 hours while water was available ad lib.

The protocol is shown on the NEXT SLIDE (2). The experimental portion of this study was conducted by the Russians. Male, Wistar rats were used. They were 63 days of age and weighed an average of 215 grams at the beginning of the experimental period. In addition to the flight group, 2 ground based controls were included. The ground control group designed to simulate flight, the flight controls, were placed in an identical spacecraft which was kept on the ground. They were exposed, as closely as possible, to the spacecraft environment and to the noise, vibration, and shock of launch and reentry. The second control group, the vivarium controls, were kept in the animal quarters under standard vivarium conditions throughout the experiment. There were two test periods, the flight period and the postflight period. Half the animals in each group were killed immediately following flight, the first 20 day test phase. The remaining rats were placed in the animal quarters and killed 25 days postflight. All rats were injected with a tetracycline derivative at the beginning of each test period and at the end of the experiment. Hence, the animals killed immediately after flight had 2 labels, an in vivo and an in vitro label encompassing the flight period, while those killed 25 days postflight had 3 labels, 2 in vivo and 1 in vitro. Tetracycline deposits

as a fluorescent label in mineralizing bone and is used to measure bone formation rate. At the end of each experimental period, the tibias were removed and frozen. They were transported frozen to the US and kept frozen until analysed. Mineralized sections were prepared from a sampling site at the tibial-fibular junction. Area, width, and surface length measurements were made using a digitizer which was interfaced with a PDP-8 computer.

The results of space flight on mean periosteal bone formation rate are shown in the NEXT SLIDE (3). The flight rats are compared with the flight controls and the vivarium controls. On the ordinate is mean periosteal bone formation rate. In this and all following slides, the vertical lines represent ± 1 SD. During flight, bone formation is decreased about 40% when compared to either control group. This decrease is highly significant with $p < 0.001$. Contributing to the decrease in formation during flight was an arrest of formation. Our evidence for a cessation of formation during flight is shown on the NEXT SLIDE (4).

Prior to this experiment, we had never seen such an extensive arrest line in rats of this age. The arrest line, which corresponds to the end of the flight period can be seen to encompass the majority of the periosteum of the flight rat; in fact, the average length of the arrest line in the flight rats was 5.3mm or 72% of the periosteal surface at the end of the flight period. This value is significantly higher than the flight control with $p < 0.001$.

How do we know this is an arrest line and not a reversal line or an artifact? The NEXT SLIDE (5) shows a higher power of a field from the tibial cross-section of the flight rat shown in the preceding slide. The left portion of the slide was photographed under Brightfield illumination while the right side is the same section using fluorescence microscopy. The reversal line is created when resorption reverses to formation; it is characterized by its irregular appearance and by acid phosphatase activity. The arrest line is created when formation ceases and is later reinitiated; unlike the reversal line, it is a smooth, distinct demarcation and does not stain for enzyme activity. The arrest line is not an artifact caused by section preparation

since the second tetracycline label, the label given at the start of the postflight period, is consistently superimposed upon this line. Also, since the second label is superimposed, bone formation must have been arrested until the end of the flight period. Although we do not know what caused the cessation, we do know that the rats were not starved since some food was found in the spacecraft following flight and that immobilization was not a factor since the flight rats, if anything, were more active than the flight controls. We don't know when arrest occurred but bone formation must have been reinitiated immediately following flight since the second label is superimposed upon the arrest line and active bone formation is required to entrap the tetracycline label. In the fluorescence photomicrograph, one can see that the distance between labels 1 and 2, which represents the width of bone formed during the 20 day flight period, is much shorter than that between the second and third labels, which is the 25 day postflight period. So, even though the animals cease forming bone during the flight, the inhibition is reversible.

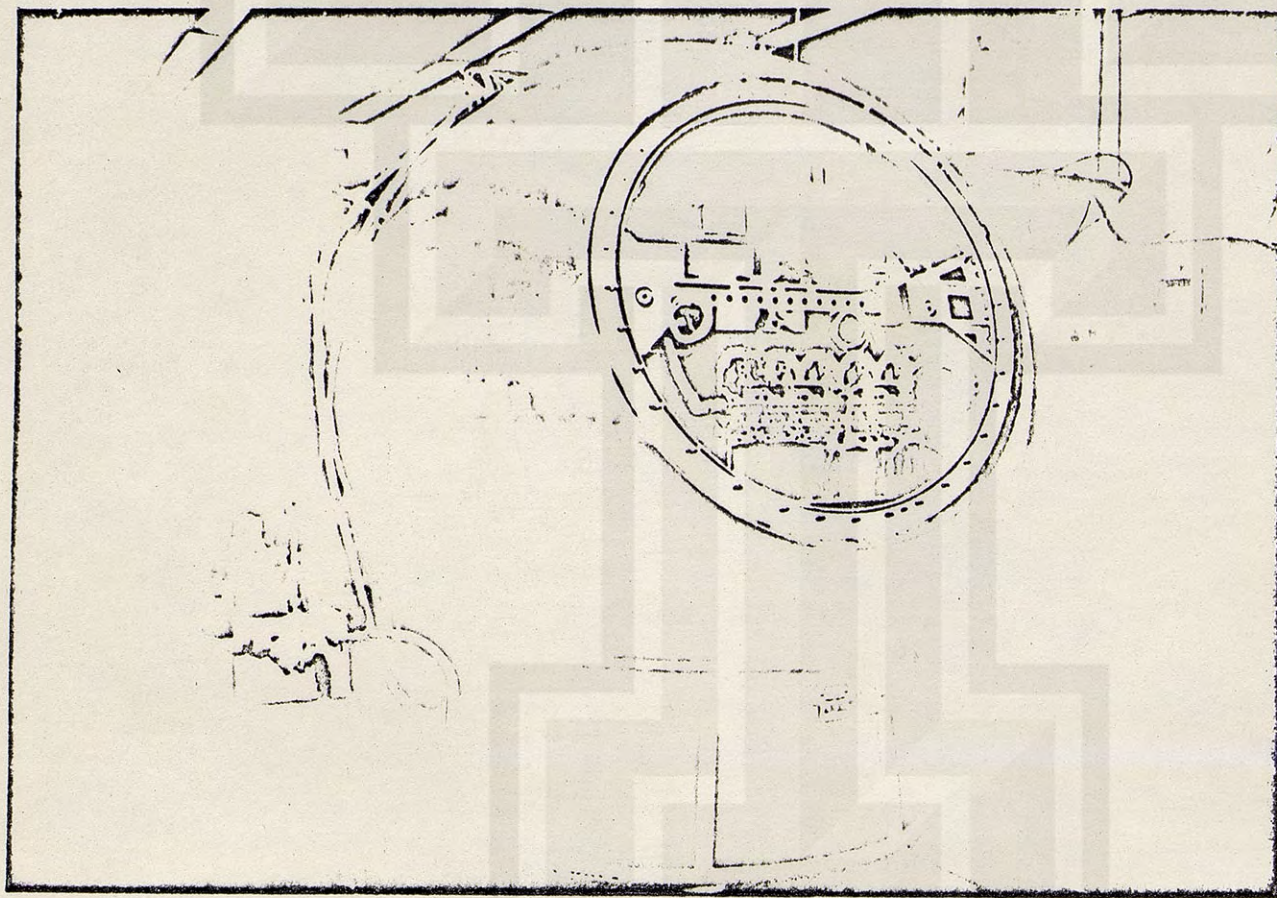
How consistent were these changes in bone formation among the individual flight rats? The NEXT SLIDE (6) shows the rate of periosteal bone formation during the flight and postflight period for each of the flight rats which was killed 25 days postflight. The horizontal lines represent the mean periosteal bone formation rate at each period. Without exception, each rat formed significantly more bone following flight than during flight; the difference is highly significant with $p < 0.001$. The first data slide showed that the flight rats formed significantly less bone during flight than either of the control groups. What about the postflight period?

NEXT SLIDE (7). During the postflight period, the flight rats show a significant increase in formation when compared to the vivarium controls with $p < 0.001$. Thus, the flight animals are not only able to correct the defect in bone formation during flight but also to show a rebound following flight. SLIDE OFF.

Bone resorption could not be quantified since formation which also occurs at the endosteum at this sampling site requires continuous tetracycline

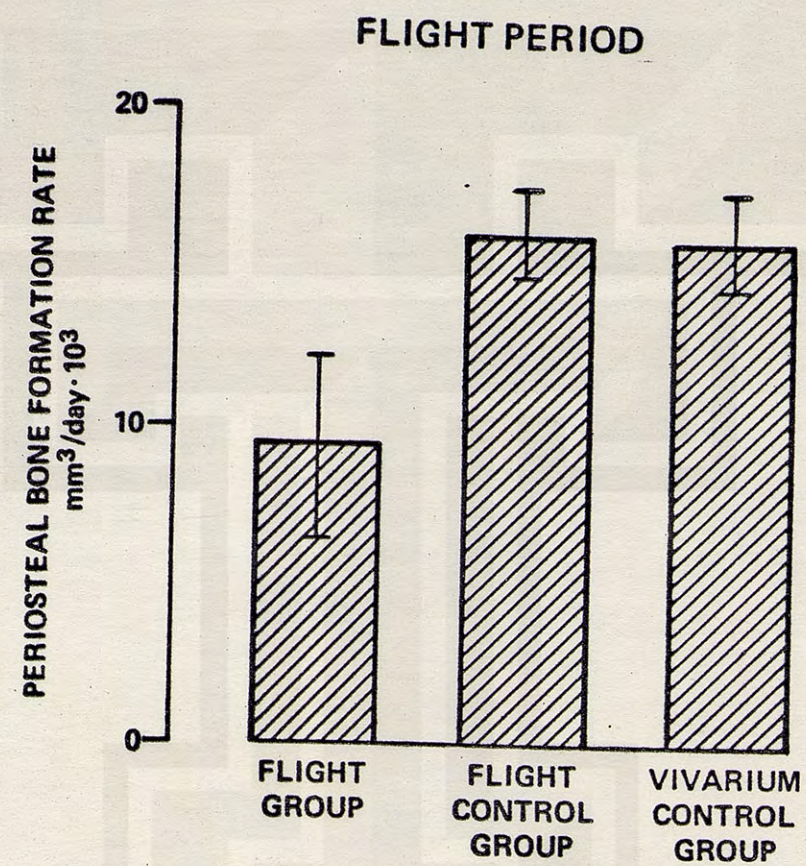
labeling for correction; continuous injections were impossible in this unmanned satellite. However, past work has shown that the medullary cavity area will enlarge to reflect any large changes in resorption since at this sampling site, resorption occurs only at the endosteum. The NEXT SLIDE (8) was not part of the flight experiment, but is used to illustrate the enlargement in medullary area in response to a strong bone resorptive stimulus. The slide shows crosssectional areas of rat tibial diaphysis. The section labeled A is from a control rat and the section labeled B is from a rat fed a low phosphate diet; this diet markedly increases bone resorption. As you can see, the medullary area not only enlarges but the endosteal surface becomes very irregular and scalloped as a result of the increased osteoclast activity; also enlarged vascular canals can be seen. In the NEXT SLIDE (9) which was shown earlier, little difference can be seen in the contour of the tibial endosteal surface or in the medullary cavity area of the flight and flight control rats. The medullary area data is shown on the NEXT SLIDE (10). No significant intergroup differences occur in the size of the medullary cavity during either experimental period. Thus, no change in bone resorption was detected.

The LAST SLIDE (11) summarizes our findings. First, no change in endosteal bone resorption was detected during either the flight or postflight period. Second, during a 20 day space flight, mean periosteal bone formation rate decreased 42%. Third, evidence from the bone sections suggests that the decrease in periosteal bone formation is due, in part, to a cessation of bone formation which occurs at some point during the flight and continues until the end of the flight period. Fourth, following flight the periosteal bone formation rate increases about 50% which is highly significant.



PROTOCOL

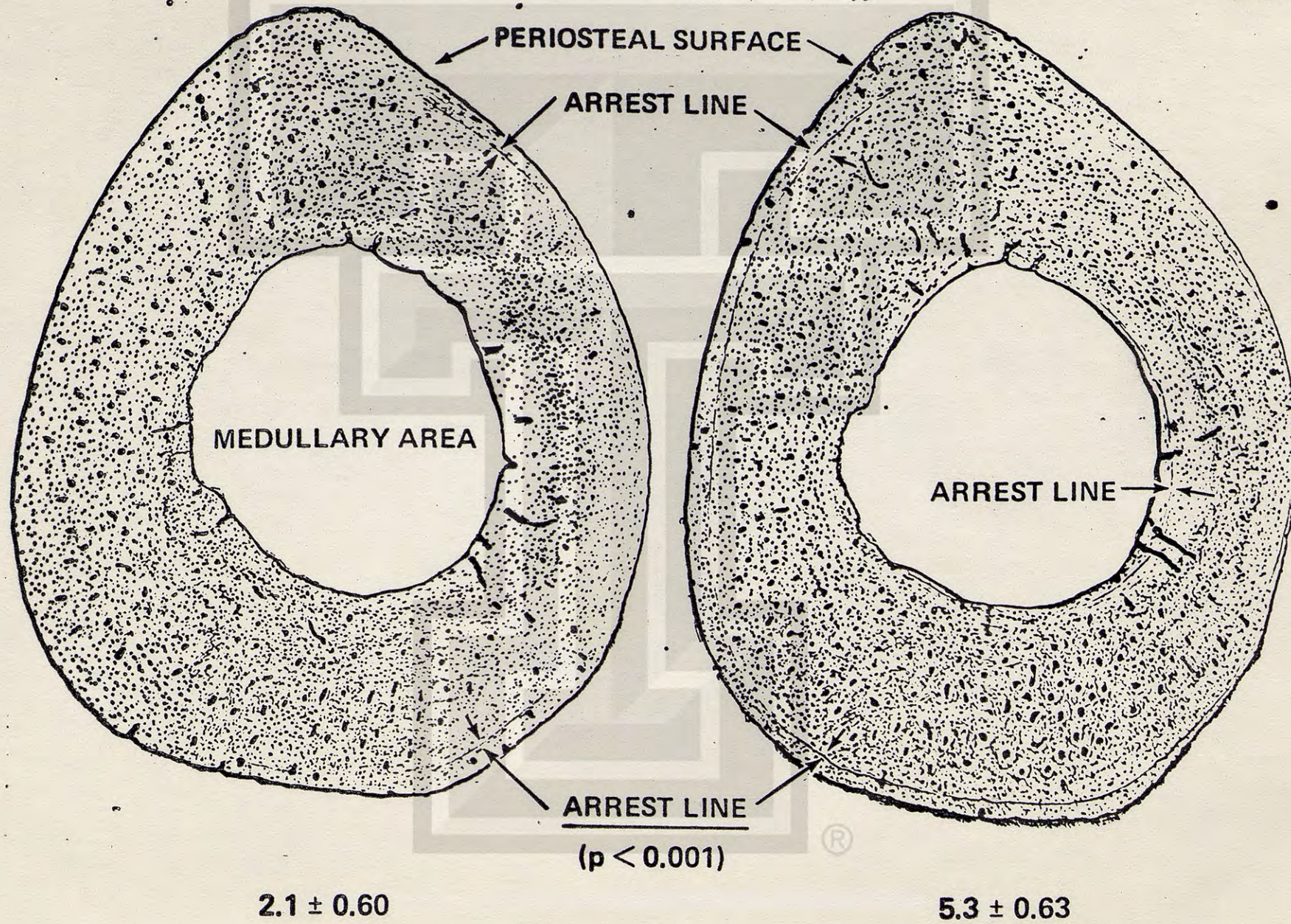
RATS:	WISTAR (MALE, 63d, 215g)
GROUPS:	FLIGHT FLIGHT CONTROL VIVARIUM CONTROL
TEST PERIODS:	FLIGHT (20d) POSTFLIGHT (25d)
TETRACYCLINE LABELS:	START OF TEST PERIOD (IN VIVO) END OF TEST PERIOD (IN VITRO)



FLIGHT

FLIGHT CONTROL RAT

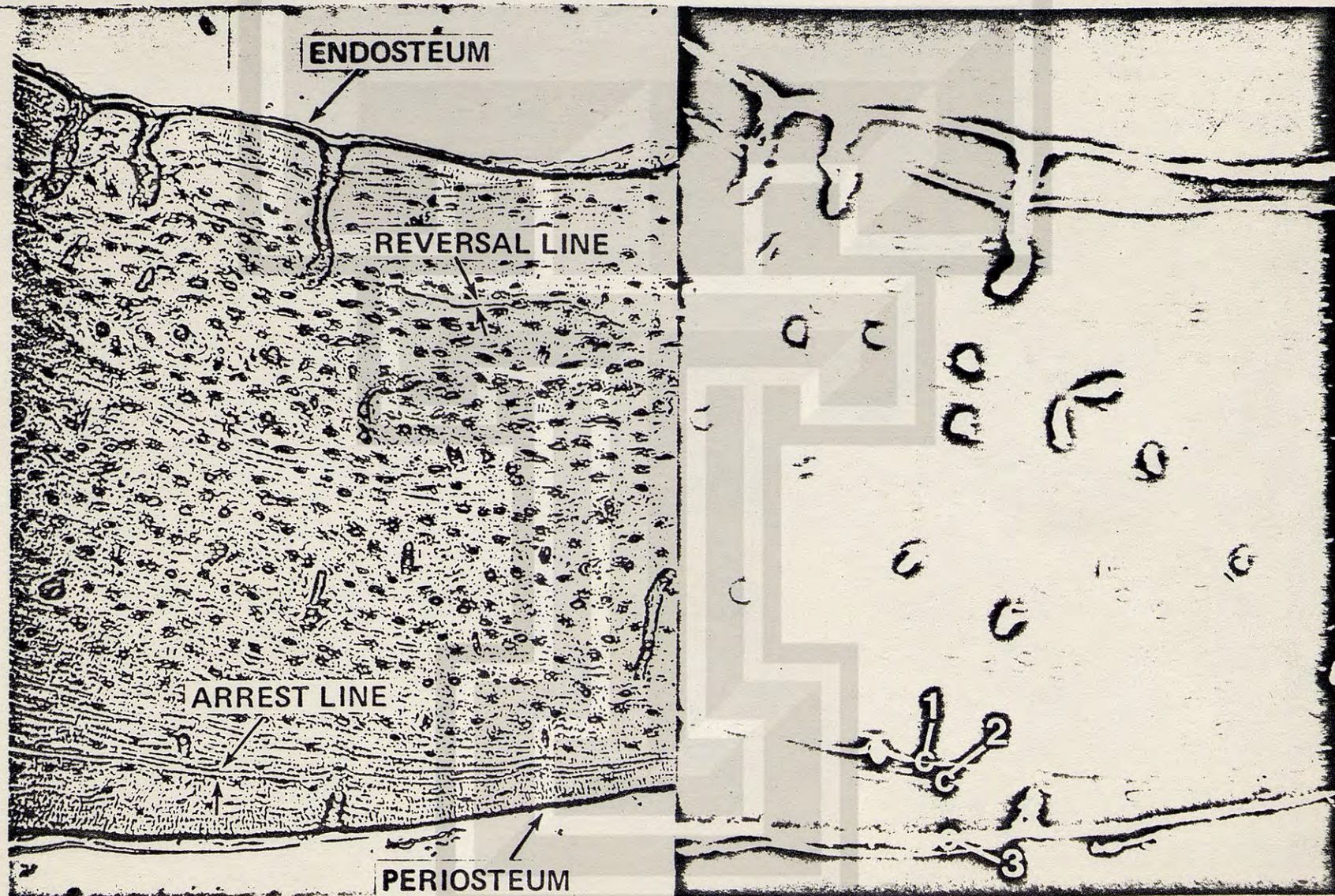
FLIGHT RAT

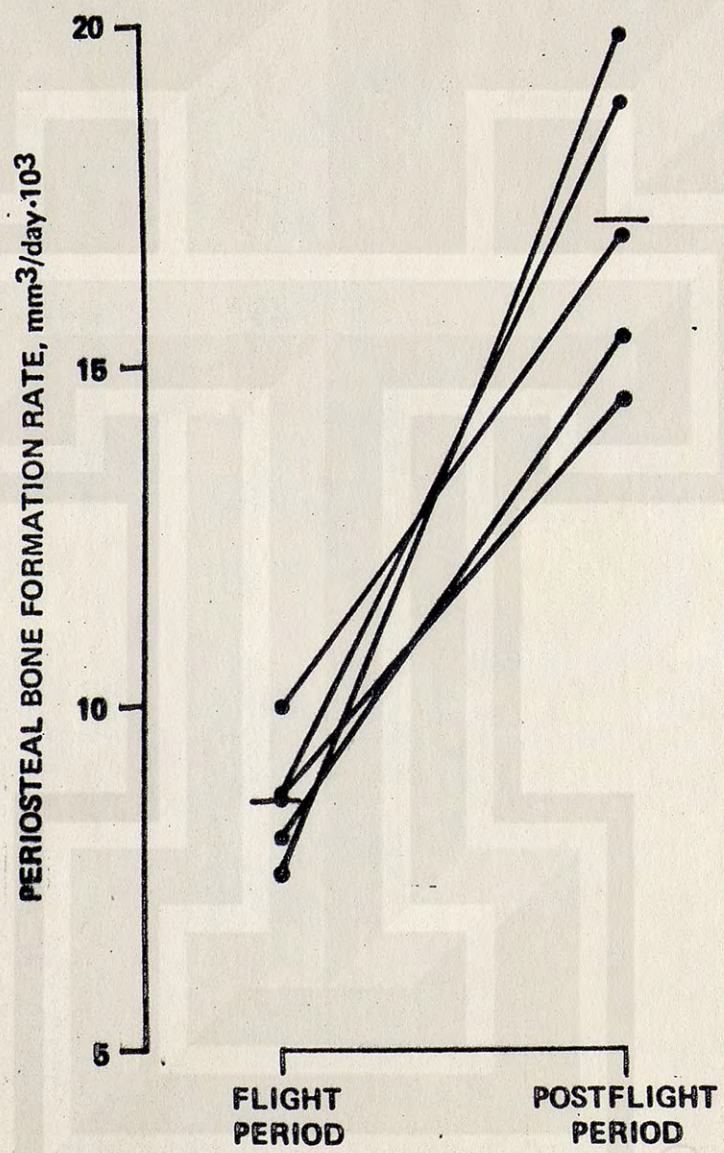


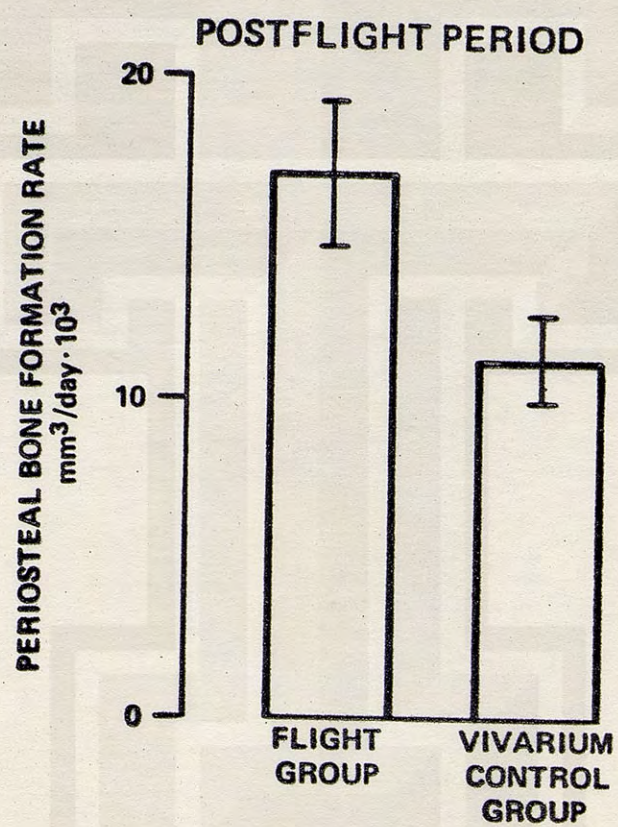
JOORESCENCE

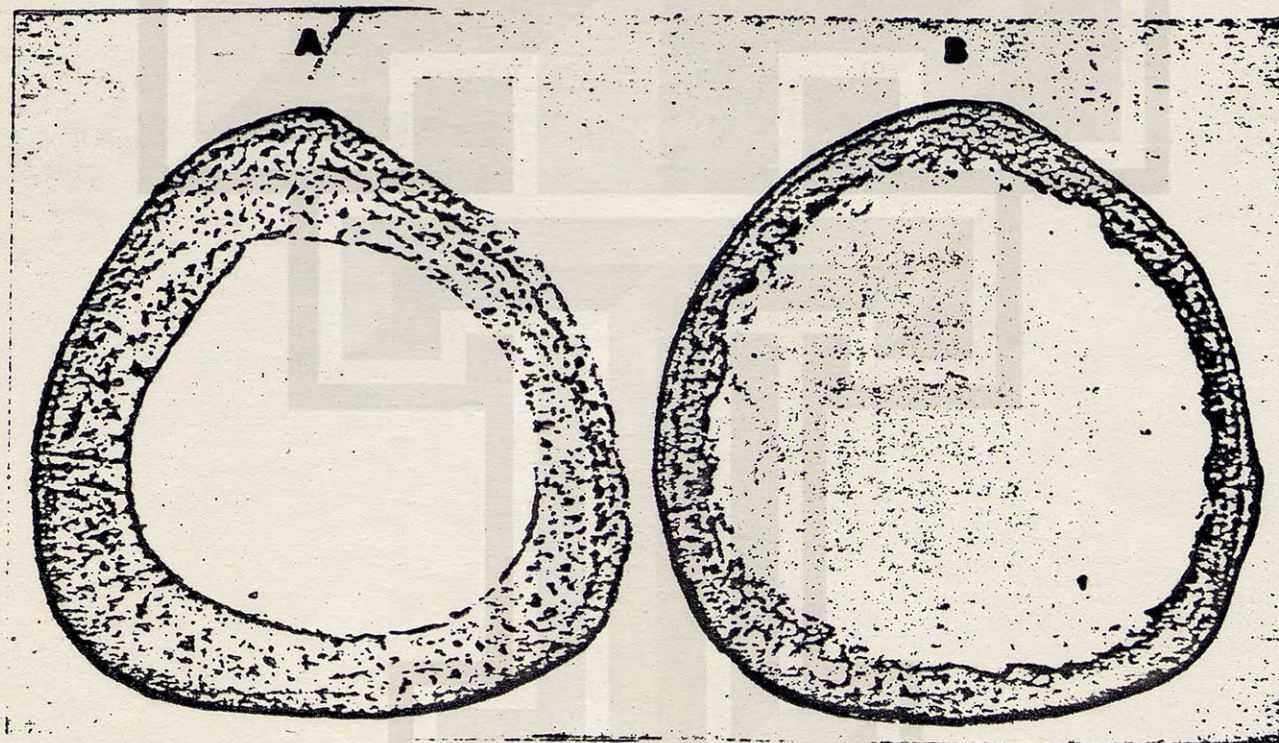
BRIGHT FIELD

FLUORESCENCE

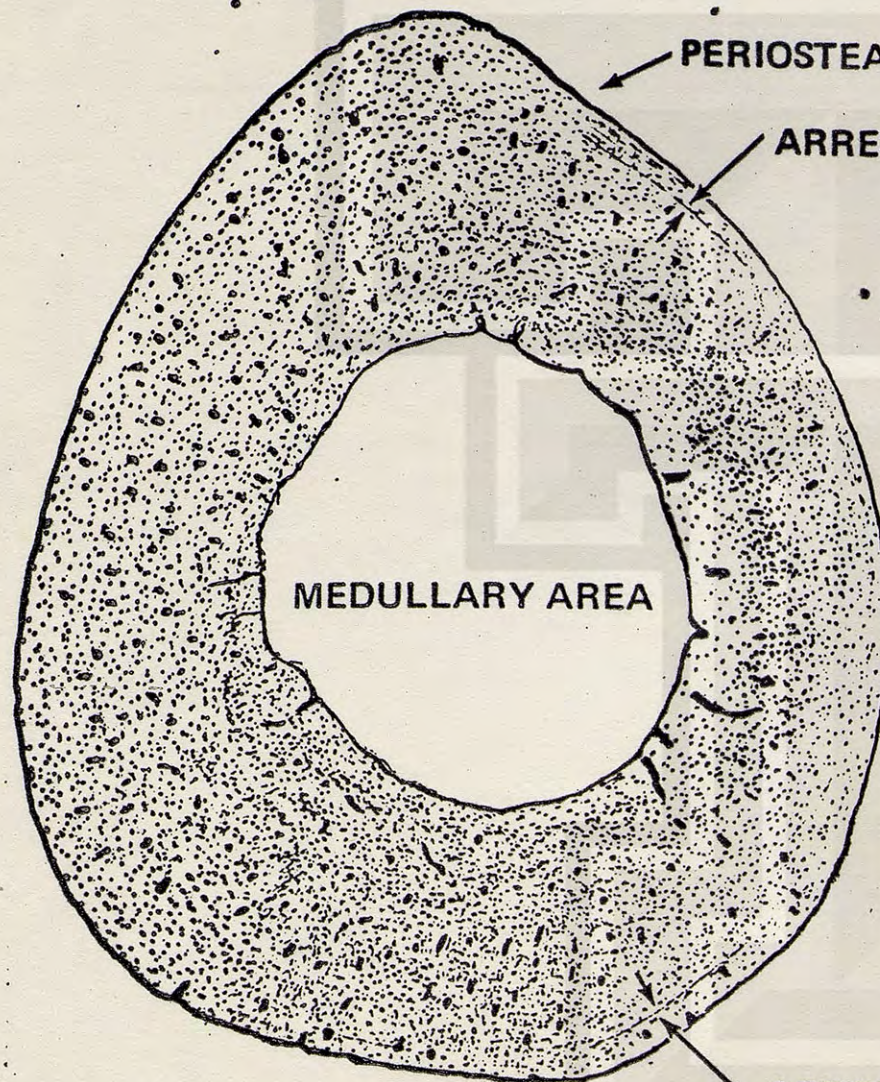






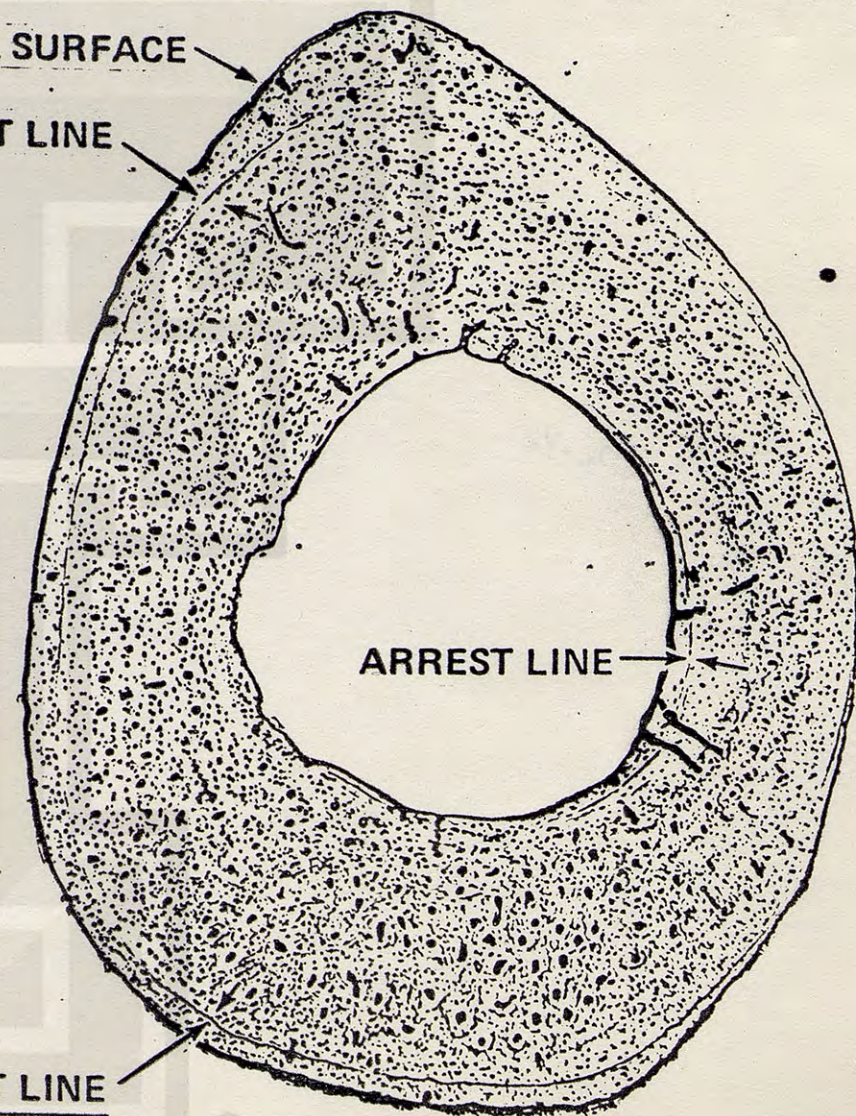


FLIGHT CONTROL RAT



2.1 ± 0.60

FLIGHT RAT



5.3 ± 0.63

PERIOSTEAL SURFACE

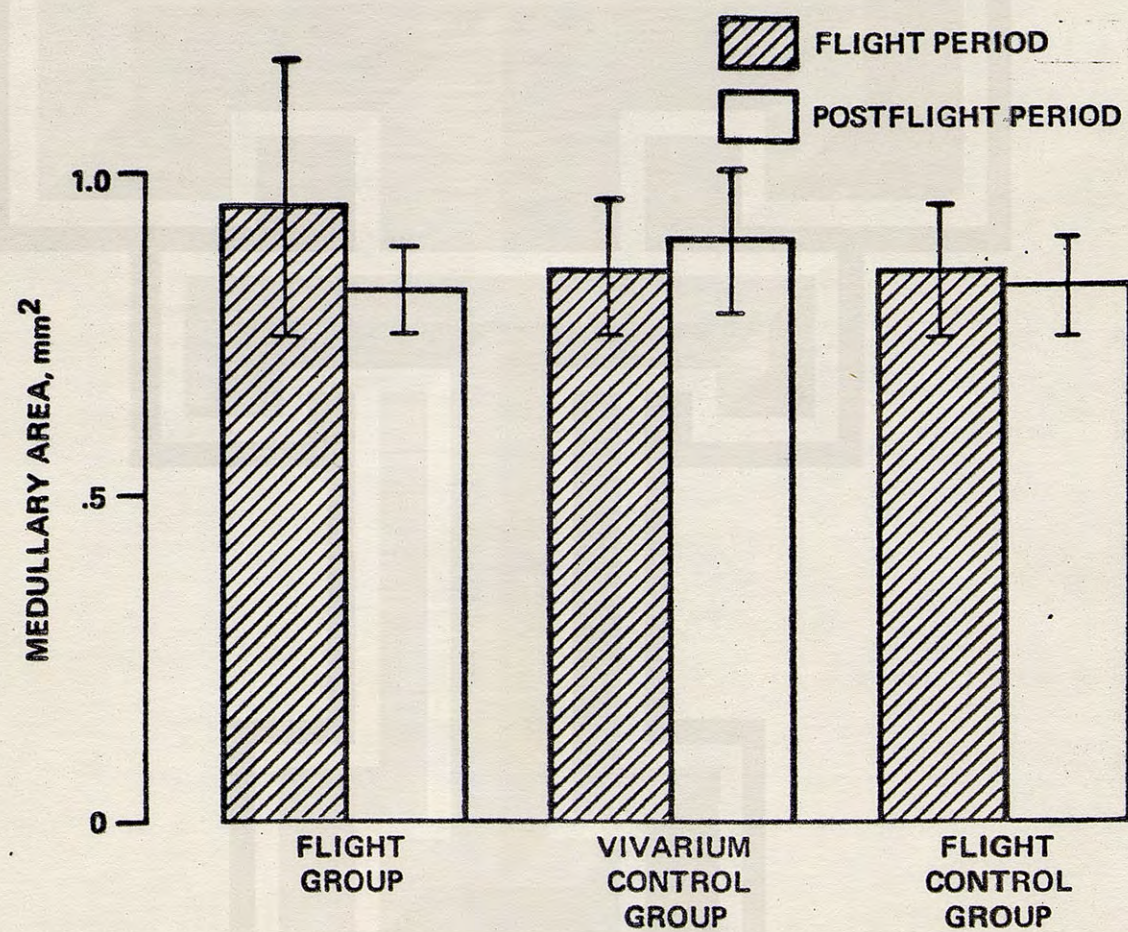
ARREST LINE

MEDULLARY AREA

ARREST LINE

ARREST LINE

($p < 0.001$)



SUMMARY

1. NO CHANGE IN ENDOSTEAL BONE RESORPTION DURING FLIGHT OR POSTFLIGHT
2. 20 DAY FLIGHT PERIOD, ↓ MEAN PERIOSTEAL BONE FORMATION RATE (42%, $p < 0.001$)
3. PERIOSTEAL BONE FORMATION ARRESTED, END OF SPACEFLIGHT
4. 25 DAY POSTFLIGHT PERIOD, ↑ MEAN PERIOSTEAL BONE FORMATION RATE

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

ROUTING SLIP

MAIL CODE	NAME	Action
		Approval
		Call Me
		Concurrence
		File
		Information
		Investigate and Advise
		Note and Forward
		Note and Return
		Per Request
		Per Telephone Conversation
		Recommendation
		See Me
		Signature
		Circulate and Destroy

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GAUMAN

NAME	TEL. NO. (or code) & EXT.
CODE (or other designation)	DATE

BONE AND CALCIUM METABOLISM

- I. BONE COMPOSITION
- II. BONE FORMATION
- III. DEPOSITION AND ABSORPTION OF BONE
- IV. CALCIUM AND PHOSPHATE METABOLISM
- V. REGULATING FACTORS
- VI. EXAMPLE BONE DISEASES

I. BONE COMPOSITION

MATRIX

COLLAGEN FIBERS

GROUND SUBSTANCE

CALCIUM SALTS

HYDROXYAPATITE XTALS (Ca , PO_4 & OH)

ADSORBED CALCIUM SALTS (EXCHANGABLE Ca) AND OTHER IONS

(BINDING AND NODULAR ARRANGEMENT $\longrightarrow$ STRENGTH & FLEXIBILITY)

II. BONE FORMATION

OSTEOBLASTS SECRETE MATRIX (CARTILAGE)

HYDROXYAPATITE XTALS PPT. WITHIN & AROUND
COLLAGEN FIBERS

GROUND SUBSTANCE ABSORBED (MOST OF IT)

III. DEPOSITION AND ABSORPTION OF BONE - A CONTINUAL PROCESS

OSTEOBLASTS → BONE DEPOSITION

OSTEOCLASTS → BONE ABSORPTION

NORMALLY, RATES ARE EQUAL THOUGH ACTIVITIES OF
EACH NOT IN THE SAME PLACE AND TIME

ADVANTAGES TO CONTINUAL PROCESS:

REPLACEMENT OF BRITTLE OLD BONE (MATRIX DEGENERATION)

REMODELING TO ADAPT TO ALTERED STRESSES

- ALTERED LINES OF FORCE
- ALTERED MAGNITUDES OF FORCE

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III. DEPOSITION AND ABSORPTION OF BONE - (Cont'd)

RATES OF DEPOSITION & ABSORPTION:

FASTER IN YOUNG; SLOWER IN OLD

DEPOSITION > ABSORPTION WITH GROWTH, INCREASED
BONE STRESS

ABSORPTION > DEPOSITION WITH DECREASED BONE
STRESS (WTL., PHYSICAL INACTIVITY), ABNORMAL
ALTERATIONS OF REGULATING FACTORS.

BONE RESPONSE TO STRESS:

COMPRESSION → PIEZOELECTRIC EFFECT →

NEGATIVE POTENTIAL AT SITE OF COMPRESSION

→ SMALL ELECT. CURRENT → OSTEOBLASTIC
STIMULATION AT NEGATIVE END

IV. CALCIUM AND PHOSPHATE METABOLISM

SOURCES

GI ABSORPTION

GI SECRETION

GI EXCRETION

URINARY EXCRETION

BODY DISTRIBUTION

LEVELS IN BLOOD AND ECF

HYPOCALCEMIA

HYPERCALCEMIA

V. REGULATING FACTORS

- EXCHANGEABLE CALCIUM (minutes to hours)

PRIMARY SOURCE: ADSORBED Ca SALTS IN BONE

- PARATHYROID HORMONE (hours to days)

FROM PARATHYROID GLANDS

STIMULATED BY DECREASED EC Ca LEVELS; INHIBITED
BY ELEVATED EC Ca

ACTS TO INCREASE EC Ca:

INCREASES OSTEOCLAST ACTIVITY (& NUMBERS)

DECREASES URINARY OUTPUT OF Ca (INCREASES URINARY
OUTPUT OF PO_4)

INCREASES GI ABSORPTION OF Ca

HIGHLY DEVELOPED HOMEOSTATIC MECHANISM; NARROW EC Ca
RANGE MAINTAINED; GLAND SIZE REFLECTS CHRONIC
ACTIVITY STATE, i.e., ATROPHY WITH BONE DISUSE

- VITAMIN D (D_2 & D_3)

ESSENTIAL FOR ABSORPTION OF Ca FROM GUT

GENERALLY, SAME EFFECTS AS PTH, BUT GREATER ON Ca
ABSORPTION; LESS ON BONE RESORPTION

ABSENCE GREATLY IMPAIRS PTH ACTION ON BONE RESORPTION

V. REGULATING FACTORS (cont.)

- CALCITONIN (minutes)

FROM THYROID GLAND IN HUMANS (THYROCALCITONIN)

STIMULATED BY ELEVATIONS OF EC Ca; INHIBITED BY
LOW EC Ca

ACTS TO SHARPLY INHIBIT BONE ABSORPTION

CAUSES DECREASE OF EC Ca

ANTAGONISTIC TO PTH

AS REGULATOR OF EC Ca:

ACTION OPPOSITE TO PTH

ACTION MUCH FASTER THAN PTH

ACTS AS A SHORT TERM REGULATOR - UNLIKE CHRONICALLY
DOMINANT PTH SYSTEM

VI. EXAMPLE BONE DISEASES

OSTEITIS FIBROSA CYSTICA - PTH XS

RICKETS - VITAMIN D INSUFF.

OSTEOMALACIA - ADULT RICKETS

OSTEOPOROSIS - DISUSE, etc.

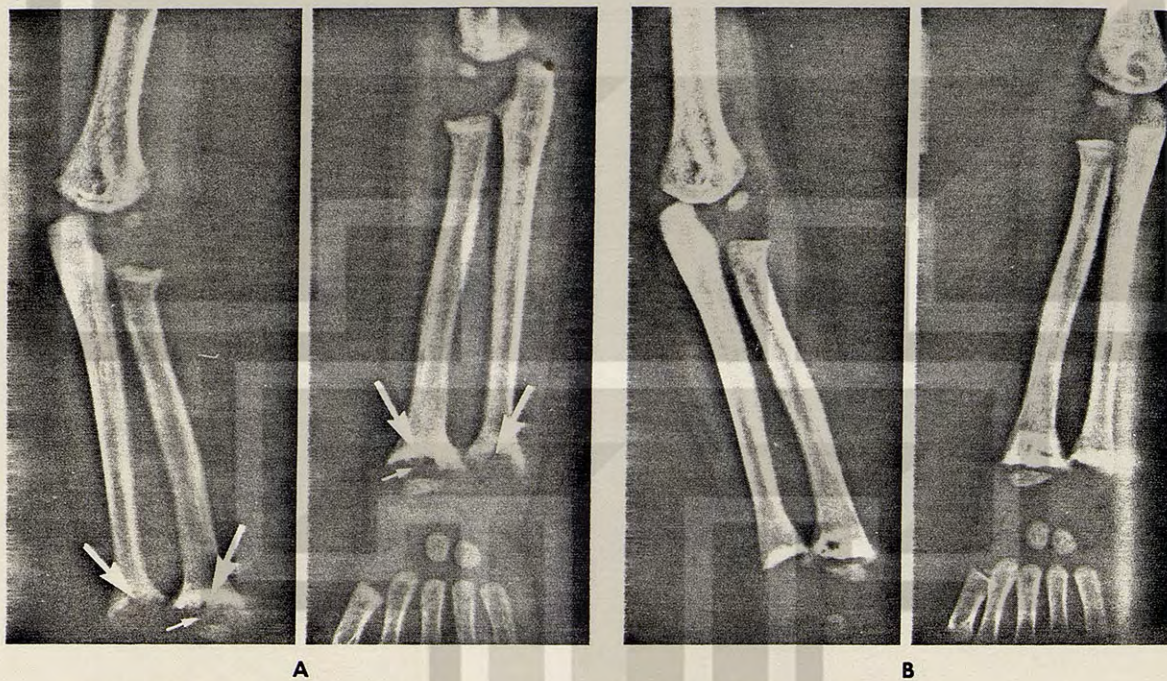


FIGURE 11-5. Vitamin D Deficiency Rickets: Active and Healing Stages.

A, The patient was two and one-half years old. Characteristic changes consequent to active rickets are demonstrated in the wrists. The metaphyses are cupped, frayed, broadened, and irregular (*large arrows*); the space between the metaphyses and epiphyses (*small arrows*) is widened—possibly the most diagnostic finding in active rickets. All the bones are demineralized to some extent and the trabeculae are coarsened; this is seen most clearly on comparison with later films.

B, Six months after vitamin D therapy, the metaphyses are less cupped and frayed, and they are narrower. Although some irregularities persist, the metaphyses will become normal with further growth.

The distance between metaphysis and epiphysis is normal, indicating disappearance of the excess noncalcified osteoid tissue, and the bones have the normal mineral density.

FIGURE 11-5
rows.

DISEASES OF BONE

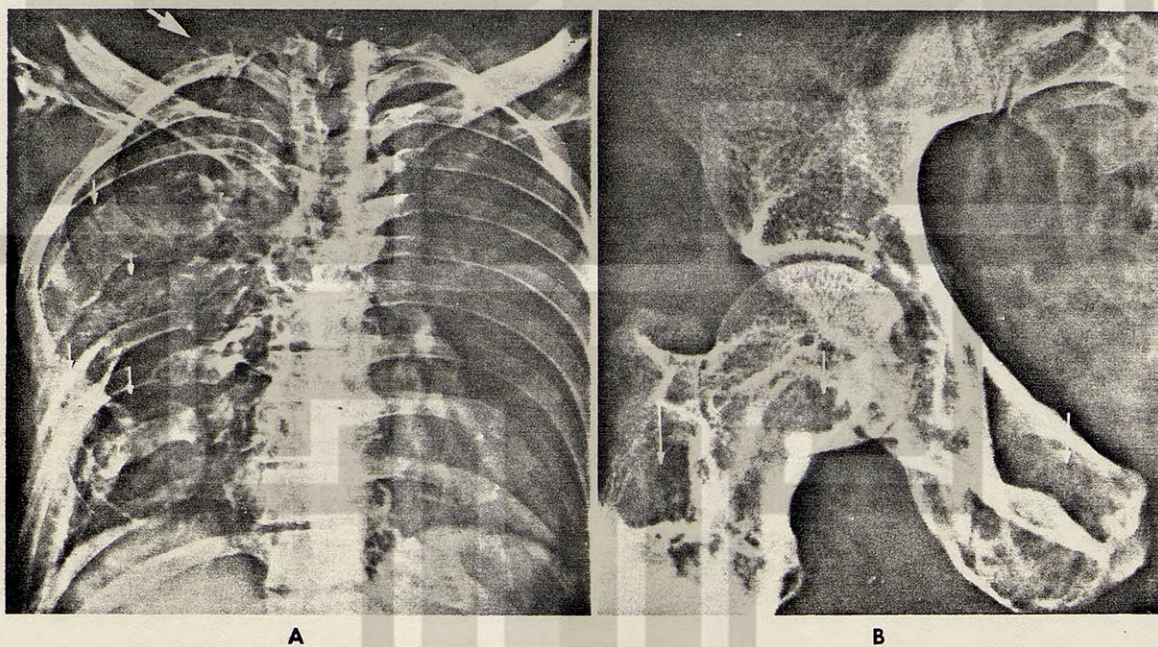


FIGURE 15-8. Osteitis Fibrosa Cystica Generalisata.

A, Posteroanterior view discloses great expansion and distortion of multiple ribs on the right (*arrows*). There is cortical thinning and loss of trabeculae. The first rib has a multicystic appearance (*large arrow*).

B, Enlarged view of the right hip area demonstrates multiple cystic lucent areas—so called brown tumors (*arrows*). There is resorption of bony trabeculae as well as cortical thinning and expansion.

The appearance closely resembles that of advanced fibrous dysplasia. Brown tumors may be single or they may be multiple and diffuse as in the present case. The serum alkaline phosphatase level is invariably elevated.

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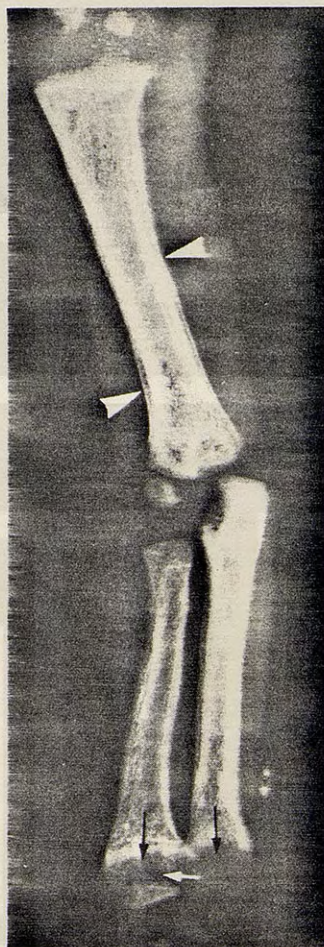


FIGURE 11-7. Active Rickets: Healing. Periosteal new bone layering is best seen in the humerus (*arrowheads*). The typical frayed cupped metaphysis (*black arrows*) and the widened space between the epiphysis and metaphysis (*white arrow*) are prominent signs.

Areas of normally calcified trabeculae have developed within the otherwise demineralized bones as a result of vitamin therapy.

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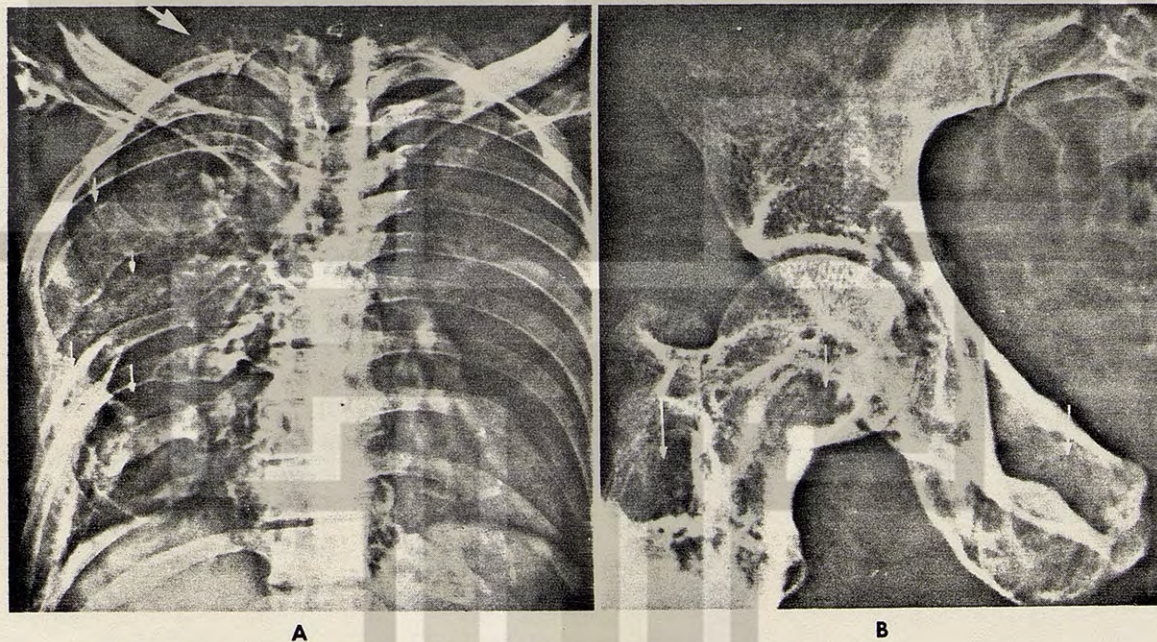


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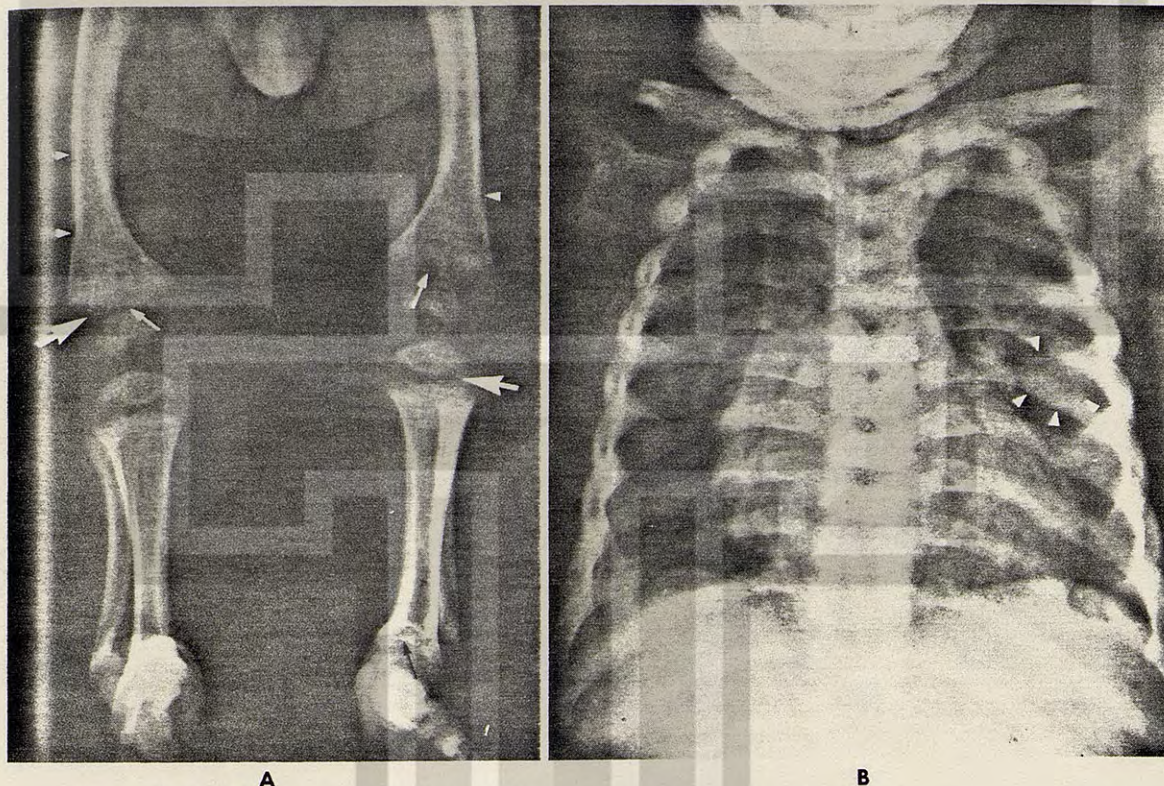


FIGURE 11-4. Advanced Rickets.

A, The long bones are demineralized, and the trabeculae are coarsened in a two-year-old child. The metaphyseal ends are broadened, frayed, and irregular (*small arrows*). The usually sharp metaphyseal line of density is absent, and the distal tibial metaphyses are cupped (*black arrow*). There is increased space between the metaphysis and epiphysis (*large arrows*). The femora are bowed, with thickened cortices medially. Periosteal layering (*arrowheads*) in the femora represents early healing with vitamin D therapy.

B, Bulbous enlargement of the anterior ends of the ribs, mainly osteoid tissue (*arrowheads*), is often seen. There is marked osseous demineralization and coarsened trabeculae.

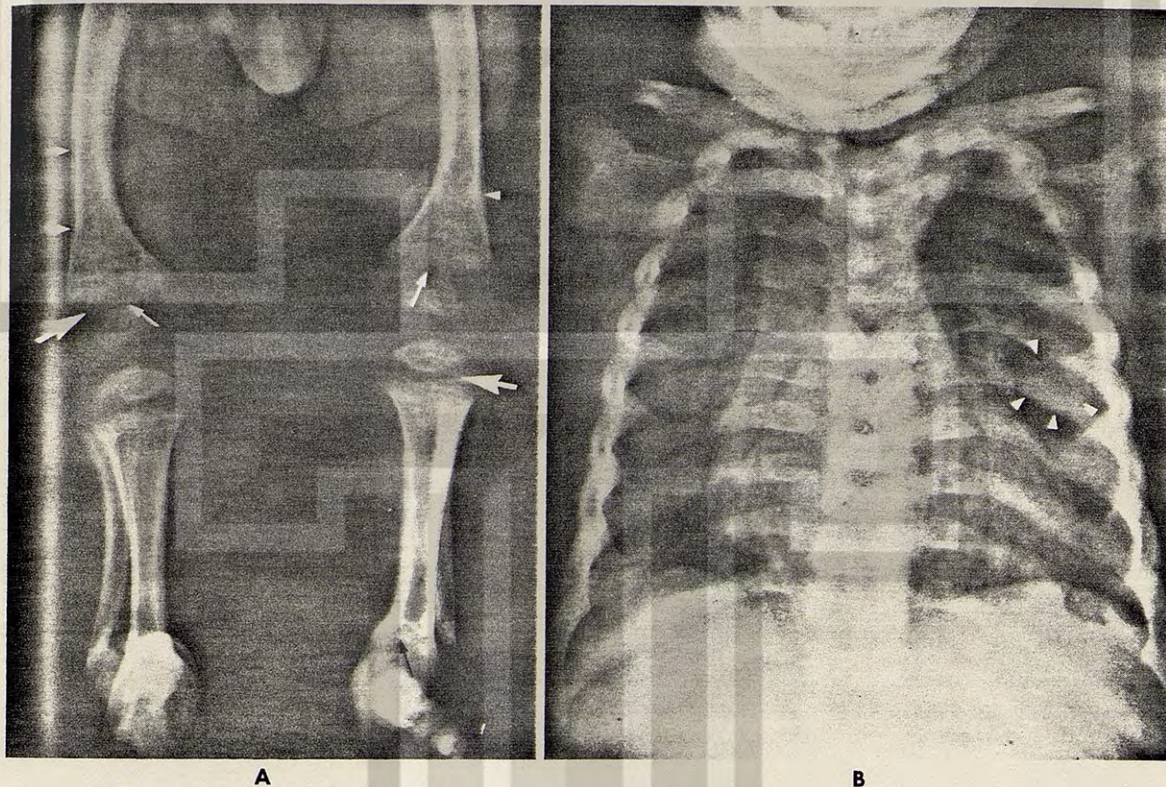


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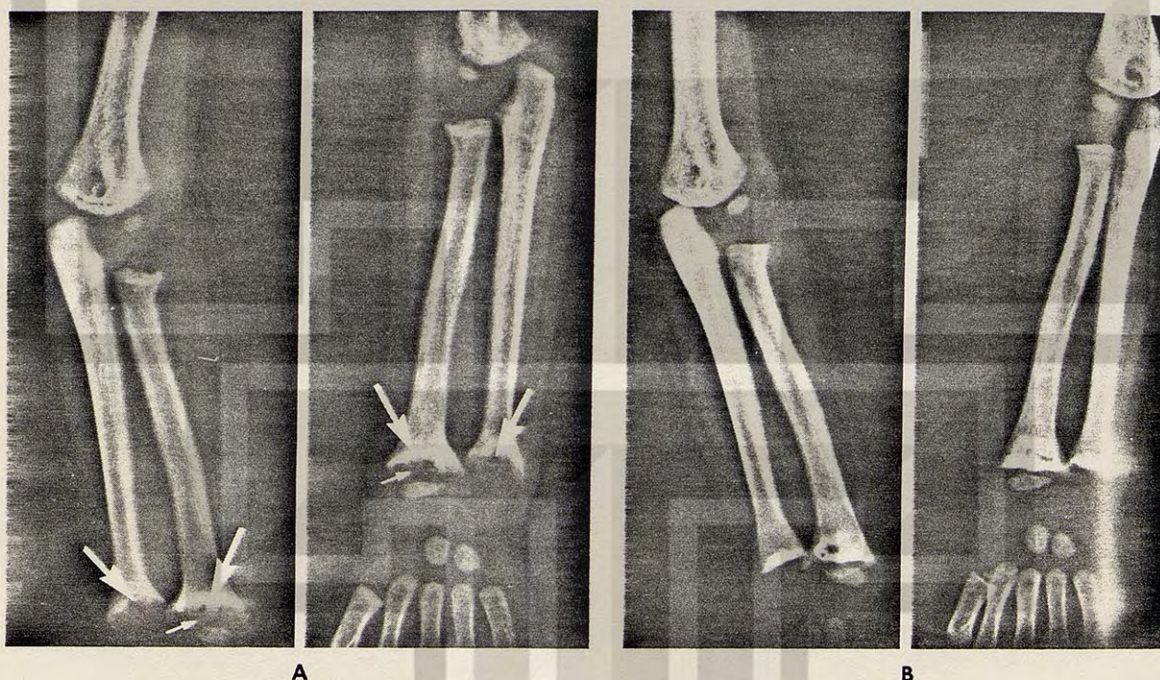


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FIGURE 11-5. Rickets, active and healing stages.

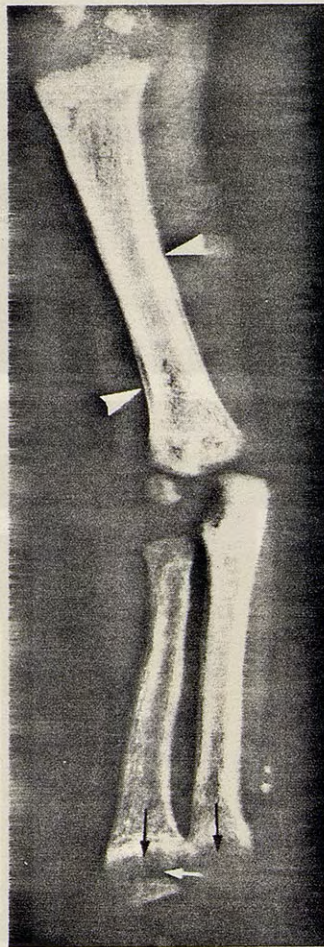


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DISEASES OF BONE

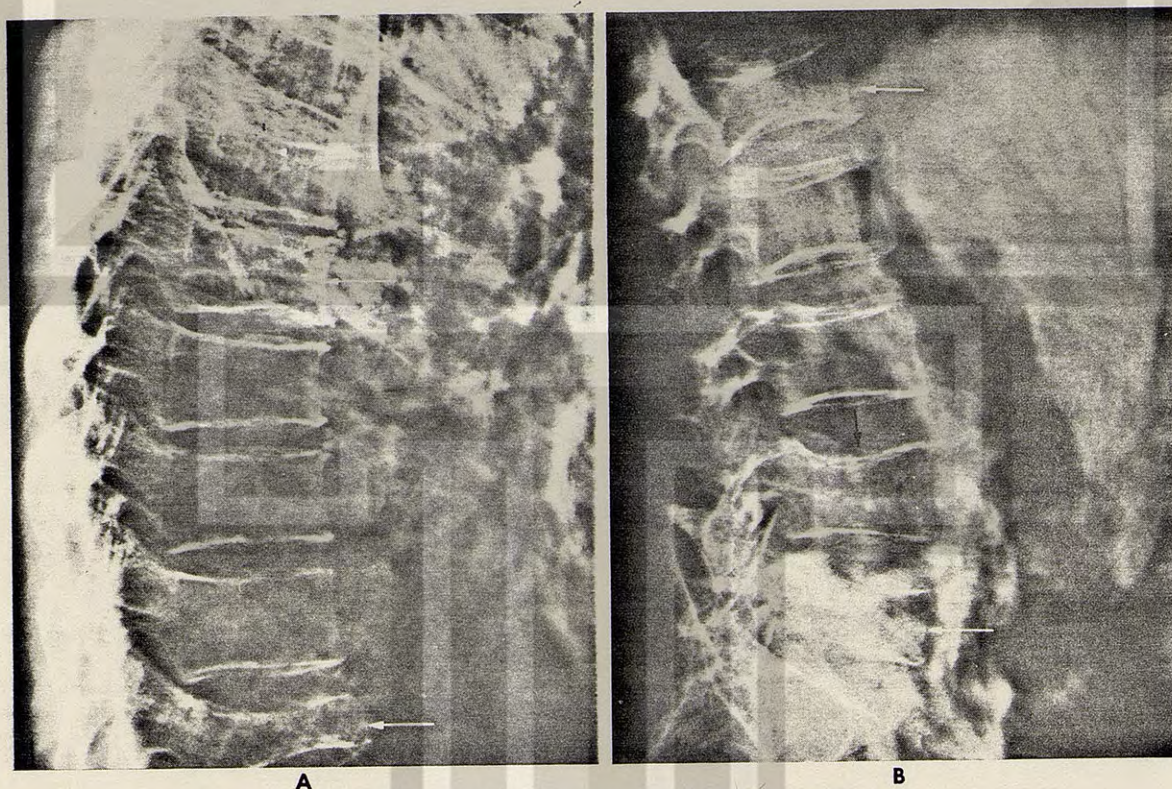


FIGURE 15-4. Osteomalacia of Spine Secondary to Malabsorption.

A, There is generalized demineralization of the spine. Two compression fractures are evident (*arrows*). The coarse striations (*arrowhead*) represent thickening of the primary trabeculae. Almost all the secondary trabeculae are completely decalcified.

B, Lateral view of the lumbar spine demonstrates two compression fractures (*white arrows*). The impression on the superior aspect of the body of L4 (*black arrow*) is due to herniation of the nucleus pulposus. The appearance is indistinguishable from that of osteoporosis.

(Courtesy of Dr. Arlyne Shockman, Veterans Administration Hospital, Philadelphia.)

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DISEASES OF BONE

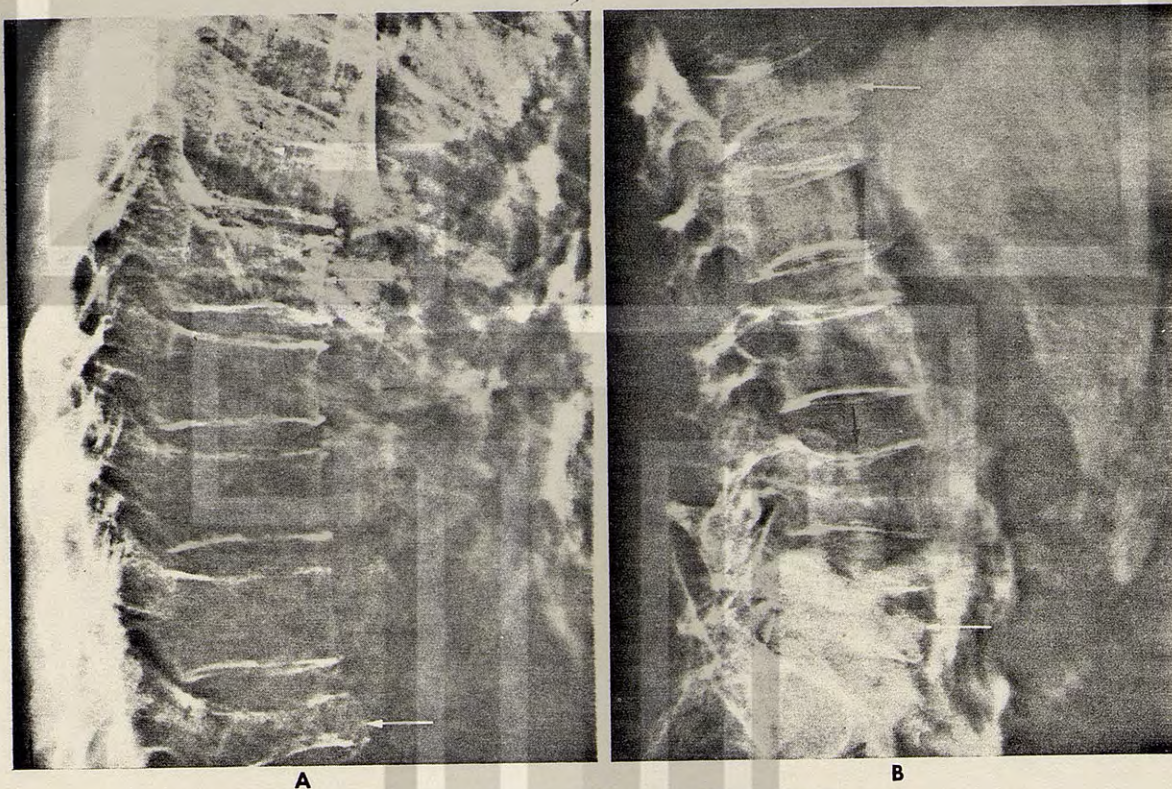


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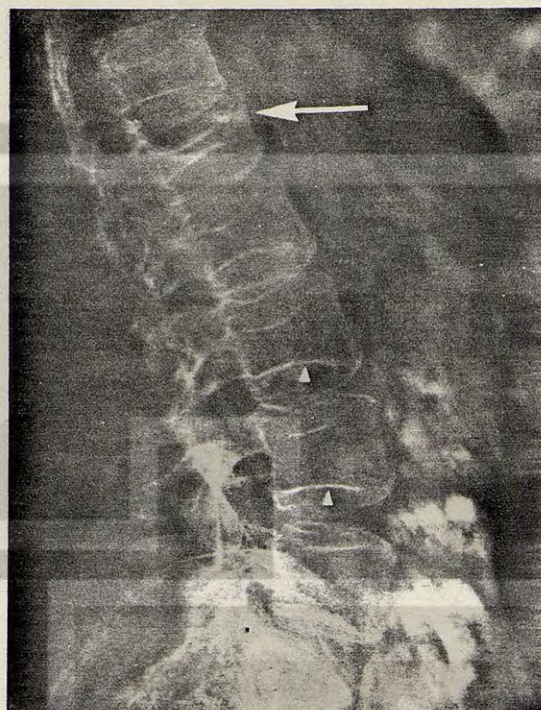


FIGURE 15-1. Senile Osteoporosis of the Lumbar Spine. The pronounced lucency of the vertebral bodies is due to extensive resorption of bony trabeculae; by contrast, the cortical end plates are thinned but appear relatively dense (*arrowheads*). There is a compression fracture of L1 (*arrow*). The densities anterior to the spine represent residual barium from a previous contrast study.

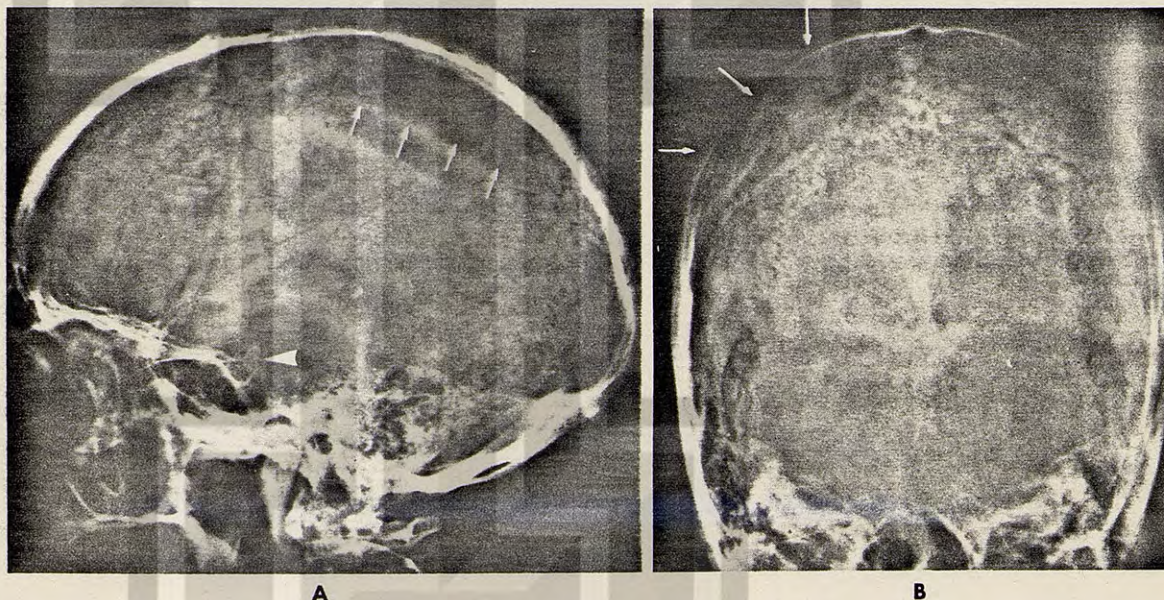


FIGURE 15-2. Osteoporosis of the Skull.

A, Lateral view discloses spotty demineralization of the calvarium causing a mottled appearance. The area of the parietal bone (*arrows*) is very much thinned. The density of the dorsum sellae and posterior clinoids is decreased (*arrowhead*).

B, In posteroanterior view the outer table in the area of the parietal bones is lacking (*arrows*) and the tables are thinned. Thinning of the parietal bones occurs rarely and usually is associated with senile or postmenopausal osteoporosis. It may also occur in younger patients with hypogonadal osteoporosis. The present patient manifested other evidence of senile osteoporosis.

(Courtesy of Dr. Arlyne Shockman, Veterans Administration Hospital, Philadelphia.)

DISEASES OF BONE

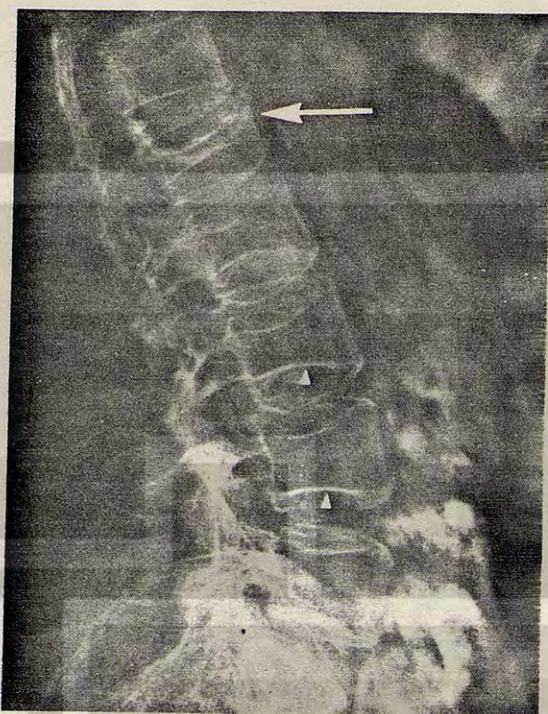


FIGURE 15-1. Senile Osteoporosis of the Lumbar Spine. The pronounced lucency of the vertebral bodies is due to extensive resorption of bony trabeculae; by contrast, the cortical end plates are thinned but appear relatively dense (*arrowheads*). There is a compression fracture of L1 (*arrow*). The densities anterior to the spine represent residual barium from a previous contrast study.

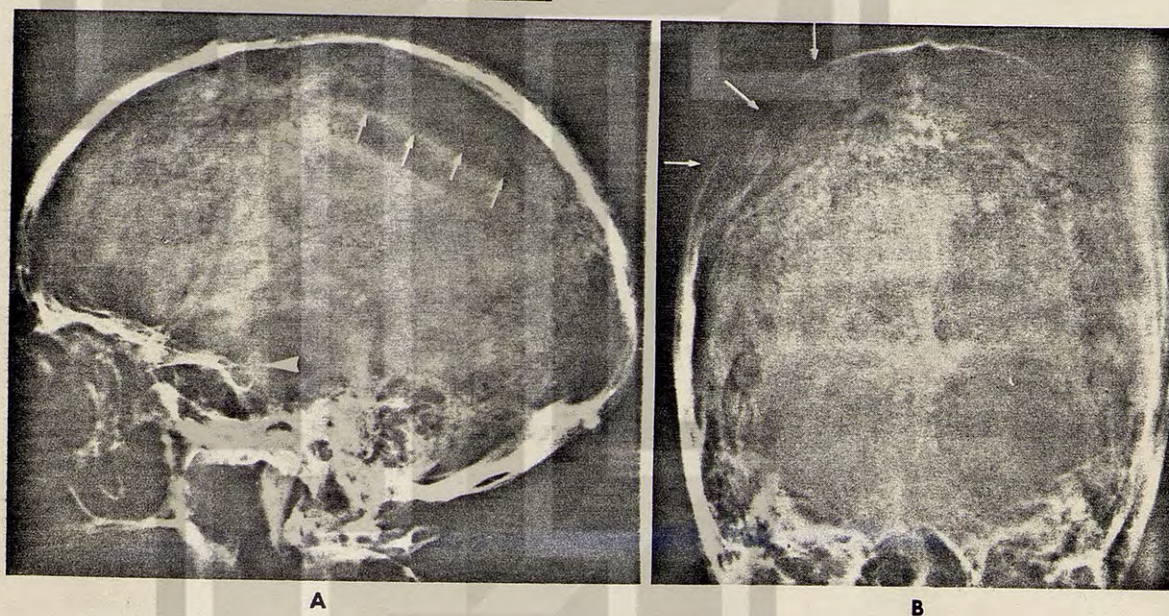


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BONE CHANGES IN SPACE FLIGHT;
PHYSIOLOGY OF THE PROBLEM

Presentation to The Administrator
Monday, December 13, 1976
11 AM

S. P. Vinograd, M.D./ SBR

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how it is formed (Fig. 3); the microscopic and gross structure of
bone, types of bone, their embryological formation, and the normal
continuing deposition and absorption of bone (Figs. 4, 4A and 4B);
factors influencing the rates of bone deposition and absorption, and
the piezoelectric response of bone to compression (Figs. 5 and 6);
calcium and phosphate metabolism (Fig. 7); the regulation of bone and
bone mineral metabolism (Figs. 8 and 9); and pathological skeletal
manifestations of certain errors of regulation (Fig. 10). The effects
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(Preferred
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AND 4C)
/ 1

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BONE AND CALCIUM METABOLISM

- I. BONE COMPOSITION
- II. BONE FORMATION
- III. DEPOSITION AND ABSORPTION OF BONE
- IV. CALCIUM AND PHOSPHATE METABOLISM
- V. REGULATING FACTORS
- VI. EXAMPLE BONE DISEASES

Fig. 1

I. BONE COMPOSITION

MATRIX

COLLAGEN FIBERS
GROUND SUBSTANCE

CALCIUM SALTS

HYDROXYAPATITE XTALS (Ca , PO_4 & OH)

ADSORBED CALCIUM SALTS (EXCHANGABLE Ca) AND OTHER IONS

(BINDING AND NODULAR ARRANGEMENT $\longrightarrow$ STRENGTH & FLEXIBILITY)

Fig. 2

II. BONE FORMATION

OSTEOBLASTS SECRETE MATRIX (CARTILAGE)
HYDROXYAPATITE XTALS PPT, WITHIN & AROUND
COLLAGEN FIBERS
GROUND SUBSTANCE ABSORBED (MOST OF IT)

III. DEPOSITION AND ABSORPTION OF BONE - A CONTINUAL PROCESS

OSTEOBLASTS $\longrightarrow$ BONE DEPOSITION

OSTEOCLASTS $\longrightarrow$ BONE ABSORPTION

NORMALLY, RATES ARE EQUAL THOUGH ACTIVITIES OF
EACH NOT IN THE SAME PLACE AND TIME

ADVANTAGES TO CONTINUAL PROCESS:

REPLACEMENT OF BRITTLE OLD BONE (MATRIX DEGENERATION)

REMODELING TO ADAPT TO ALTERED STRESSES

- ALTERED LINES OF FORCE

- ALTERED MAGNITUDES OF FORCE

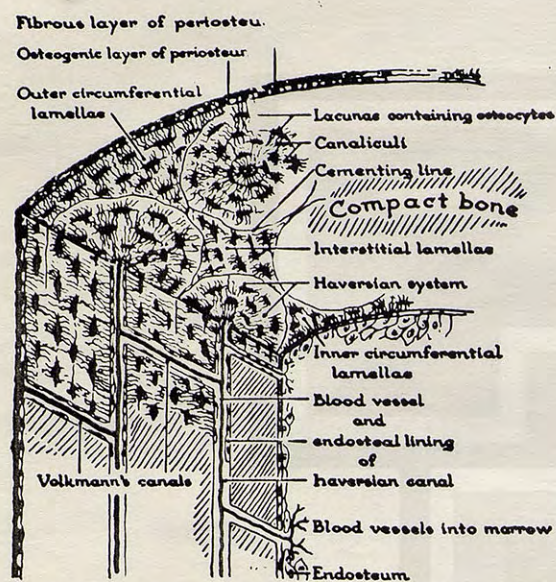


FIG. 160. A three-dimensional diagram showing the appearance of both a cross section and a longitudinal section of the shaft of a mature long bone. This diagram shows the relationship between the blood vessels of the periosteum, Volkmann's canals, Haversian canals and the marrow cavity.

Fig. 5

How Haversian systems can be added to older shafts

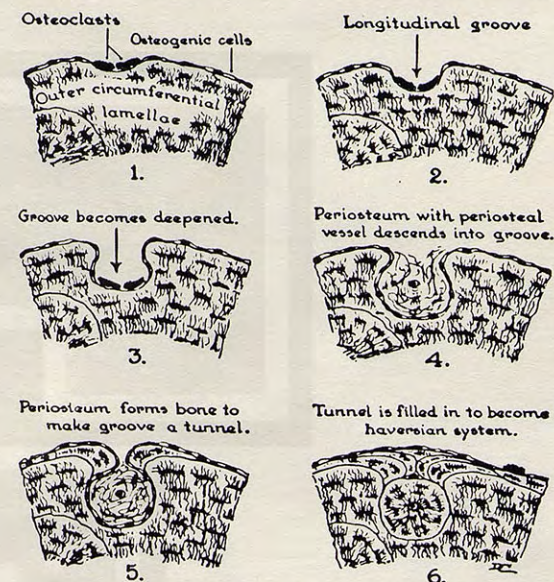


FIG. 158. Diagrams of cross sections of the shaft of a bone showing how Haversian systems are laid down under the periosteum in older bones to replace outer circumferential lamellae.

Fig. 6

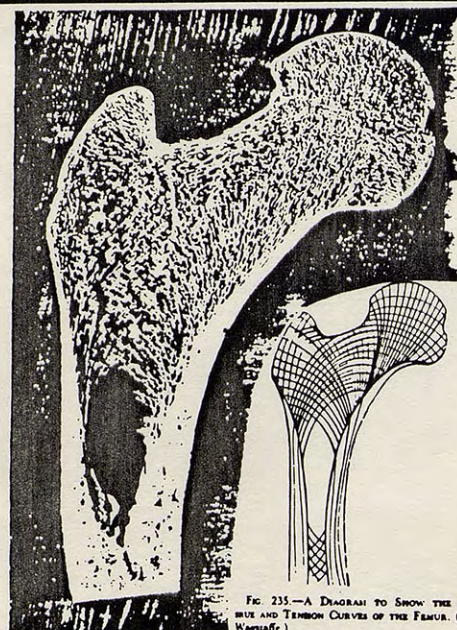


FIG. 235.—A DIAGRAM TO SHOW THE PIEZOELECTRIC AND TENSION CURVES OF THE FEMUR. (After Wagstaff.)

327. Right thigh bone, femur, upper extremity, ground frontal section, from in front.

Fig. 7

III. DEPOSITION AND ABSORPTION OF BONE - (Cont'd)

RATES OF DEPOSITION & ABSORPTION:

FASTER IN YOUNG; SLOWER IN OLD

DEPOSITION > ABSORPTION WITH GROWTH, INCREASED BONE STRESS

ABSORPTION > DEPOSITION WITH DECREASED BONE STRESS (WTL., PHYSICAL INACTIVITY), ABNORMAL ALTERATIONS OF REGULATING FACTORS

BONE RESPONSE TO STRESS:

COMPRESSION → PIEZOELECTRIC EFFECT →
NEGATIVE POTENTIAL AT SITE OF COMPRESSION
→ SMALL ELECT. CURRENT → OSTEOBLASTIC
STIMULATION AT NEGATIVE END

III. DEPOSITION AND ABSORPTION OF BONE - (Cont'd)

LACK OF COMPRESSION (OR DECREASE) →
DECREASED OSTEOBLASTIC ACTIVITY;
OSTEOCLASTIC ACTIVITY CONTINUES AT NORMAL
RATE → NET BONE ABSORPTION

BONE IS A LIVING TISSUE - MAINTAINED BY AND
RESPONSIVE TO ACTIVITY; ATROPHYING WITH
DISUSE.

Fig. 9

IV. CALCIUM AND PHOSPHATE METABOLISM

SOURCES
GI ABSORPTION
GI SECRETION
GI EXCRETION
URINARY EXCRETION
BODY DISTRIBUTION
LEVELS IN BLOOD AND ECF
HYPOCALCEMIA
HYPERCALCEMIA

Fig. 10

V. REGULATING FACTORS

- EXCHANGEABLE CALCIUM (minutes to hours)
PRIMARY SOURCE: ADSORBED Ca SALTS IN BONE
- PARATHYROID HORMONE (hours to days)
FROM PARATHYROID GLANDS
STIMULATED BY DECREASED EC Ca LEVELS; INHIBITED
BY ELEVATED EC Ca
ACTS TO INCREASE EC Ca:
INCREASES OSTEOCLAST ACTIVITY (& NUMBERS)
DECREASES URINARY OUTPUT OF Ca (INCREASES URINARY
OUTPUT OF PO_4)
INCREASES GI ABSORPTION OF Ca
HIGHLY DEVELOPED HOMEOSTATIC MECHANISM; NARROW EC Ca
RANGE MAINTAINED; GLAND SIZE REFLECTS CHRONIC
ACTIVITY STATE, I.E., ATROPHY WITH BONE DISUSE
- VITAMIN D (D_2 & D_3)
ESSENTIAL FOR ABSORPTION OF Ca FROM GUT
GENERALLY, SAME EFFECTS AS PTH, BUT GREATER ON Ca
ABSORPTION; LESS ON BONE RESORPTION
ABSENCE GREATLY IMPAIRS PTH ACTION ON BONE RESORPTION

V. REGULATING FACTORS (cont.)

- CALCITONIN (minutes)
FROM THYROID GLAND IN HUMANS (THYROCALCITONIN)
STIMULATED BY ELEVATIONS OF EC Ca; INHIBITED BY
LOW EC Ca
ACTS TO SHARPLY INHIBIT BONE ABSORPTION
CAUSES DECREASE OF EC Ca
ANTAGONISTIC TO PTH
AS REGULATOR OF EC Ca:
ACTION OPPOSITE TO PTH
ACTION MUCH FASTER THAN PTH
ACTS AS A SHORT TERM REGULATOR - UNLIKE CHRONICALLY
DOMINANT PTH SYSTEM

VI. EXAMPLE BONE DISEASES

OSTEITIS FIBROSA CYSTICA - PTH XS

RICKETS - VITAMIN D INSUFF.

OSTEOMALACIA - ADULT RICKETS

OSTEOPOROSIS - DISUSE, etc.

SYNOPSIS ON BONE & MUSCLE CHANGES
UNDER WEIGHTLESSNESS CONDITIONS

PREPARED BY
THE OFFICE OF LIFE SCIENCES
NASA HEADQUARTERS

MAY 16, 1977

BONE & MUSCLE CHANGES

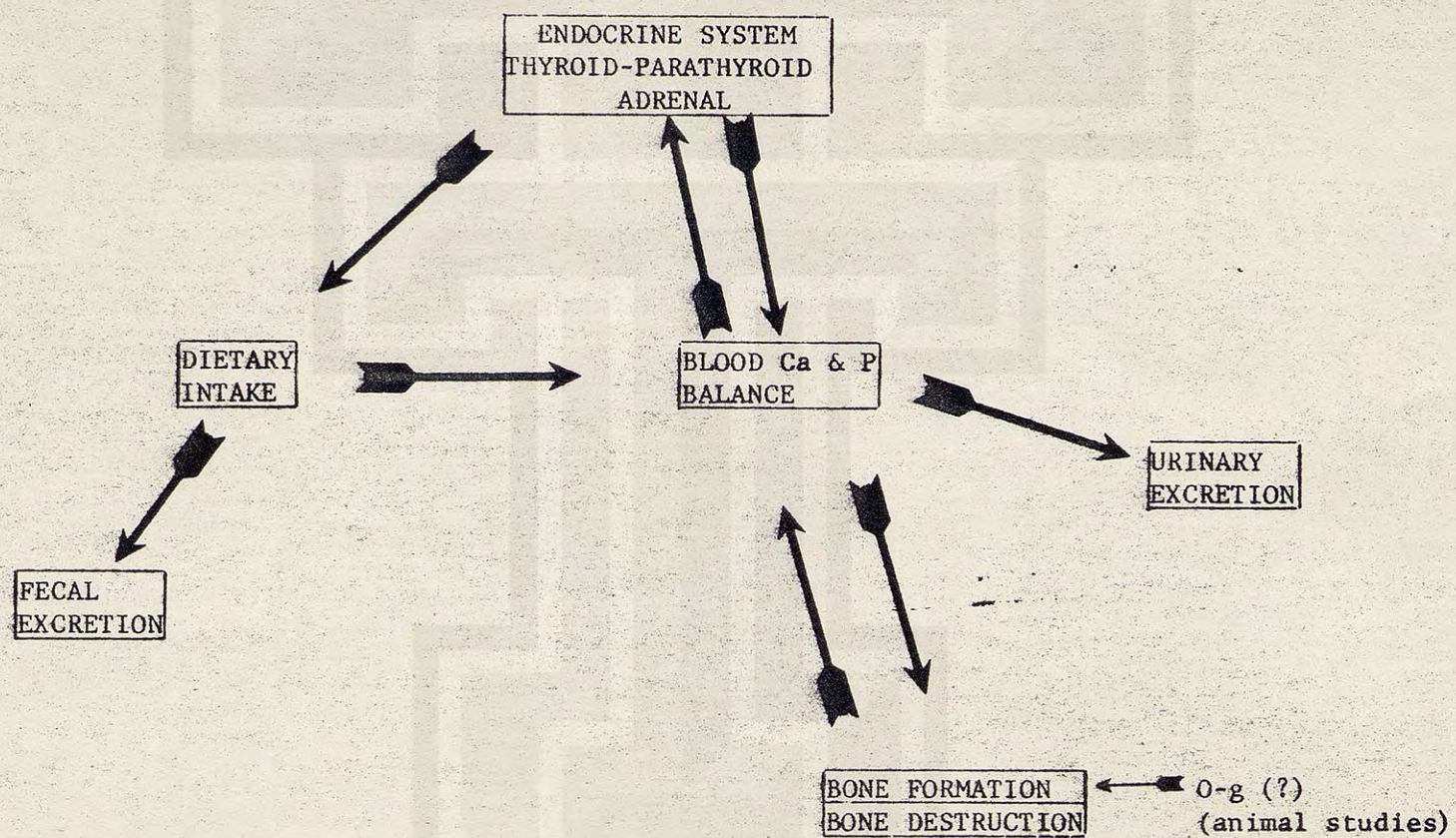
BACKGROUND

SIGNIFICANCE FOR SHUTTLE

APPROACHES TO THE PROBLEM

FUTURE EFFORTS

CALCIUM & BONE METABOLISM



BACKGROUND
(BONE CHANGES)

- O THE OCCURRENCE OF CALCIUM LOSS IN SPACE FLIGHTS
HAS BEEN REPEATEDLY DEMONSTRATED FROM GEMINI
THROUGH SKYLAB
- O THE CESSATION OF BONE FORMATION HAS BEEN OBSERVED
IN WISTAR RATS DURING THE RECENT JOINT USA-USSR
BIOSATELLITE SPACE FLIGHT (KOSMOS 782, NOV. 1975)
- O GROUND BASED STUDIES (BED REST) HAVE BEEN FOUND
TO PARALLEL CHANGES IN BONE DENSITY AND URINARY
CALCIUM EXCRETION RATES INDUCED BY SPACE FLIGHTS.

TECHNIQUES UTILIZED IN THE MEASUREMENT OF MINERAL LOSS

O SKELETAL MINERAL LOSS

- UPPER EXTREMITY (RADIUS, ULNA)
- LOWER EXTREMITY (Os CALCIS)
- METHOD (PRE AND POST FLIGHT ONLY)

RADIOGRAPHIC DENSITOMETRY
(GEMINI 4, 5, 7 AND APOLLO 6, 7, 8)

PHOTON ABSORPTIOMETRY
(APOLLO 14, 15, 16 AND SKYLAB 2,3,4)

O INFLIGHT URINARY MINERAL LOSS (SKYLAB ONLY)

- CALCIUM & PHOSPHORUS
- HYDROXY PROLINE (BONE MATRIX INVOLVED IN CALCIUM FIXATION)
- ELECTROLYTES (P, Mg, Mn, etc. INVOLVED IN CALCIUM BONE METABOLISM)

MANNED SPACE FLIGHTS

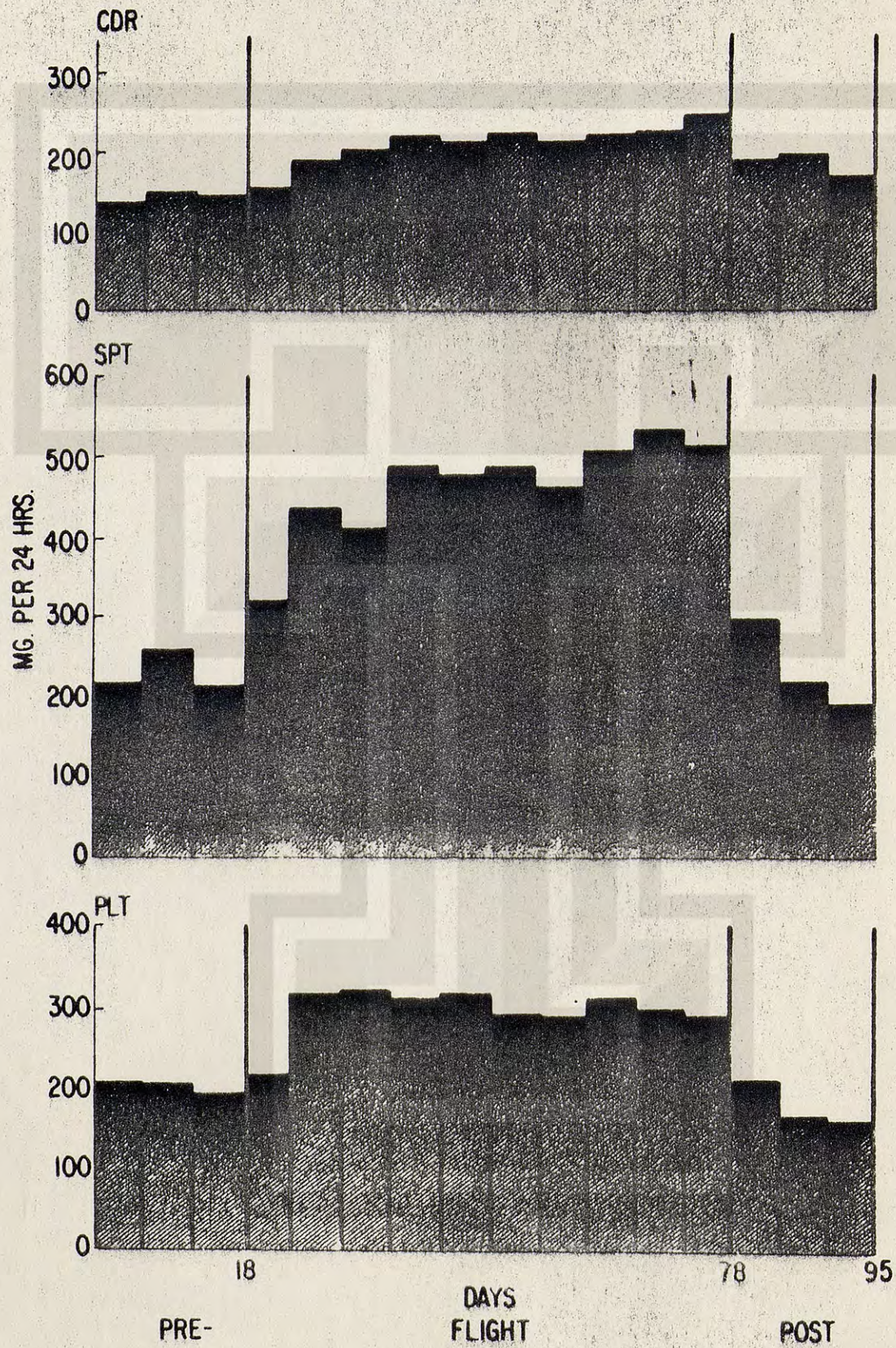
- O CONCERNS EXPRESSED PRIOR TO MERCURY PROGRAM ABOUT POSSIBLE KIDNEY STONES (URINARY Ca EXCRETION) OR BONE FRACTURES FOLLOWING LOSS OF BONE MASS (Ca LOSS) IN 0-g AND EXPOSURE TO REENTRY G-FORCES
- O RADIOGRAPHIC ESTIMATES ON BONE MINERAL LOSS (OS CALCIS) IN GEMINI 4, 5 AND 7 CREWMEN FROM 2-6% (TECHNIQUE EMPLOYED NOT ACCURATE & PRODUCED SIGNIFICANT OVERESTIMATION OF Ca LOSS)
- O APOLLO DATA ON BONE MINERAL LOSS VARIABLE AND DIFFICULT TO INTERPRET SINCE SOME OF THE CREW MEMBERS WERE EXPOSED TO LUNAR GRAVITY
- O SKYLAB DATA SHOWED A 7.4%, 4.5% AND 7.9% DECREASE BONE MINERAL CONTENT (OS CALCIS) IN THE SL-3 SCIENTIST PILOT, AND SL-4 SCIENTIST PILOT AND PILOT RESPECTIVELY

MANNED SPACE FLIGHT
SKYLAB URINE FINDINGS

- O DURING SKYLAB 3 THE SCIENTIST PILOT DOUBLED HIS URINARY CALCIUM EXCRETION WHEREAS THE COMMANDER AND PILOT ONLY INCREASED 50% OF PREFLIGHT LEVEL (ONLY SCIENTIST PILOT HAS OS CALCIS MINERAL LOSS)
- O DURING SKYLAB 4 URINARY CALCIUM MORE THAN DOUBLED DURING FLIGHT IN THE PILOT, INCREASED BY 65% IN THE SCIENTIST PILOT AND INCREASED BY 60% IN THE COMMANDER. Os CALCIS MINERAL LOSSES OCCURRED IN THE SAME ORDER, i.e., GREATEST IN THE PILOT
- O URINARY HYDROXYPROLINE EXCRETION (INDICATIVE OF BONE TURNOVER AND BREAKDOWN) INCREASED INFLIGHT. THE MEAN INCREASE WAS 33%

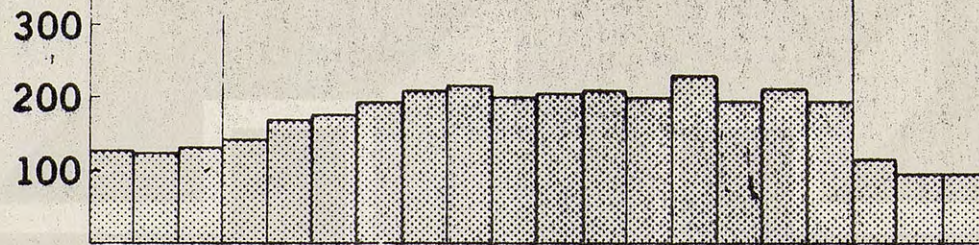
URINARY CALCIUM, SKYLAB-3

17-21720



URINARY CALCIUM, SKYLAB-4

CDR

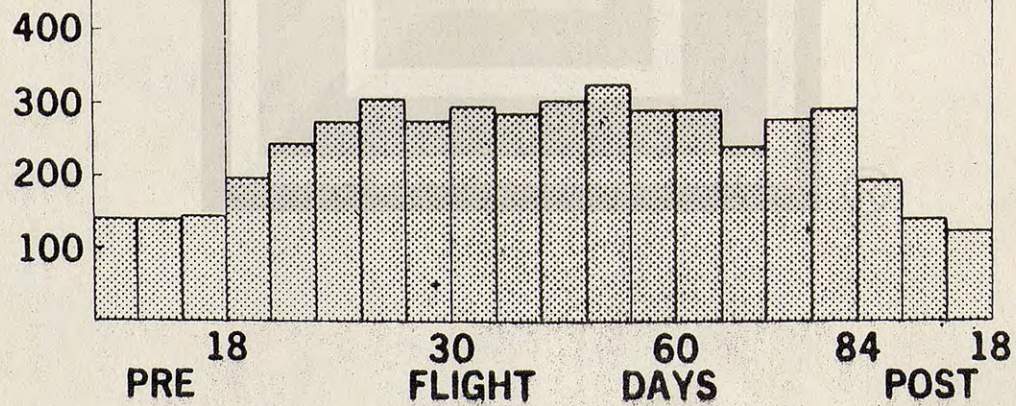


SPT

MG PER 24 HRS



PLT



S-17-21716

ANIMAL STUDIES (KOSMOS 782)

- O NO EVIDENCE IN INCREASED BONE DESTRUCTION RATES WAS DETECTED EITHER DURING THE FLIGHT OR POST FLIGHT PERIOD IN MATURE RATS
- O DURING A 20-DAY SPACE FLIGHT, MEAN BONE FORMATION RATE DECREASED BY 42%
- O EVIDENCE FROM THE BONE SECTIONS SUGGESTS THAT THE DECREASE IN BONE FORMATION IS DUE IN PART, TO A CESSATION OF BONE FORMATION WHICH OCCURS AT SOME POINT DURING THE FLIGHT AND CONTINUES UNTIL THE END OF THE FLIGHT PERIOD
- O FOLLOWING FLIGHT THE BONE FORMATION RATE INCREASES ABOUT 50%

BED REST EXPERIENCE AS RELATED TO SKYLAB MISSIONS

(BONE CHANGES)

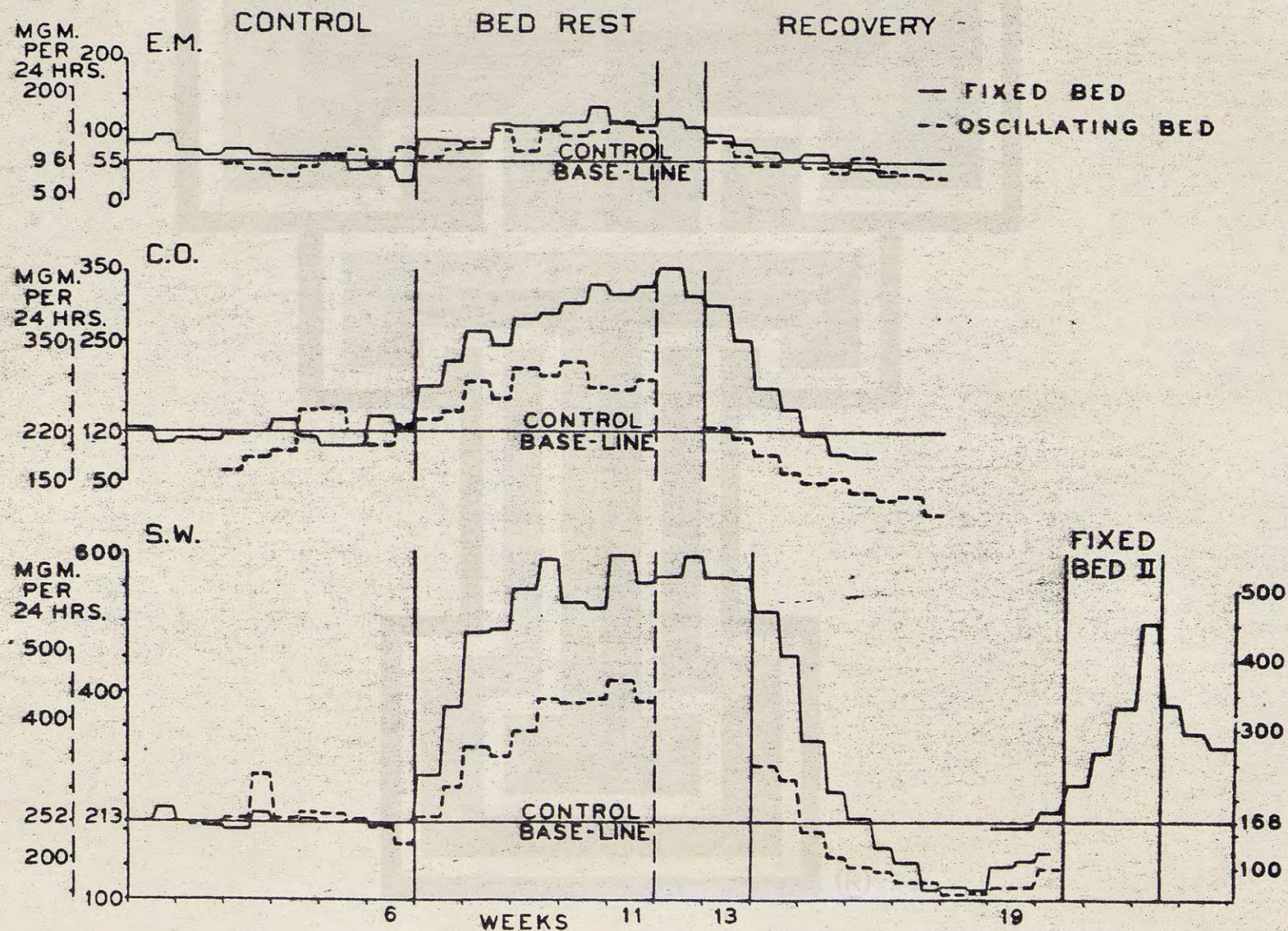
- O CALCIUM BALANCES ARE SIMILAR FOR A 30 DAY PERIOD WITH 0.3% BEING LOST ON THE FIRST SKYLAB MISSION AND 0.5% BEING LOST DURING A COMPARABLE PERIOD OF BED REST
- O MINERAL LOSS FROM THE OS CALCIS WAS NOT EVIDENT DURING THE 28-DAY FIRST SKYLAB MISSION, NOR AFTER A SIMILAR PERIOD OF BED REST
- O MINERAL LOSSES FROM THE OS CALCIS DURING THE 59-DAY MISSION FELL WITHIN THE LIMITS SET BY THE BED REST EXPERIENCE, i.e., $-7.0 \pm 5.5\%$
- O MINERAL LOSSES FROM THE OS CALCIS DURING THE 84-DAY MISSION FELL WITHIN THE LIMITS SET BY THE BED REST EXPERIENCE, i.e., $11.2 \pm 7.3\%$
- O IN NEITHER SITUATION WERE MINERAL LOSSES SEEN IN THE RADIUS OR ULNA (UPPER EXTREMITY)
- O OF THE NINE CREWMEN STUDIED, ONLY 4 HAD PREDICTION TERMS WITHIN THE RANGE OF THE BEDRESTED SUBJECTS. THE OS CALCIS MINERAL CHANGES OBSERVED IN THESE FOUR CREWMEN FELL WITHIN THE PREDICTED LIMITS

BED REST EXPERIENCE AS RELATED TO SKYLAB MISSIONS

(URINE CALCIUM EXCRETION)

- O THE NEGATIVE SHIFT IN CALCIUM BALANCE (LOSS) IN THE SIX SKYLAB 2 & 3 CREWMEN WAS OF THE SAME MAGNITUDE AND SIMILAR TO SKYLAB 4 CREW
- O INCREASES IN URINARY CALCIUM LOSS DURING SPACE FLIGHT AND IN-FLIGHT CHANGES IN CALCIUM BALANCE ARE CLOSELY. SIMILAR IN DEGREE TO THOSE FOUND IN BED RESTED SUBJECTS
- O SIMILARITY OF BED REST IN PATTERN OF URINARY CALCIUM INCREASES AND OF TOTAL CALCIUM SHIFTS SUGGEST THAT CALCIUM LOSSES WOULD CONTINUE OVER LONG PERIOD OF TIME. (APPROXIMATELY 4 GRAMS/ MONTHS OR 0.3 TO 0.4% OF TOTAL BODY CALCIUM PER MONTH)

URINARY CALCIUM EXCRETION IMMOBILIZATION IN FIXED AND OSCILLATING BEDS



CALCIUM BALANCE

Skylab vs. Immobilized Bed Rest
(mg/day)

	<u>Ambul.</u> <u>control</u>	<u>In-flight</u> <u>(bed rest)</u>	<u>Shift</u>
SL-2,3 (mean, 6 astros)	+90	-94*	-184
Immobil. (mean, 4 subjs)	+126	-154*	-280
*(after 1st 12 days)			

BACKGROUND

(MUSCLE CHANGES)

- O INDIRECT EVIDENCE OF ANTIGRAVITY MUSCLES WASTING
FOLLOWING SPACE FLIGHTS (LOWER EXTREMITIES)

- O SIMILAR MUSCLE CHANGES ARE OBSERVED IN BEDRESTED
SUBJECTS

TECHNIQUES UTILIZED IN THE MEASUREMENT OF
MUSCLE CHANGES

O PHYSICAL MEASUREMENTS

- MUSCLE COORDINATION TESTS
- MUSCLE ELECTRICAL ACTIVITY STUDIES
- CALF SIZE MEASUREMENTS
- WEIGHT MEASUREMENTS
- MUSCLE STRENGTH TESTING

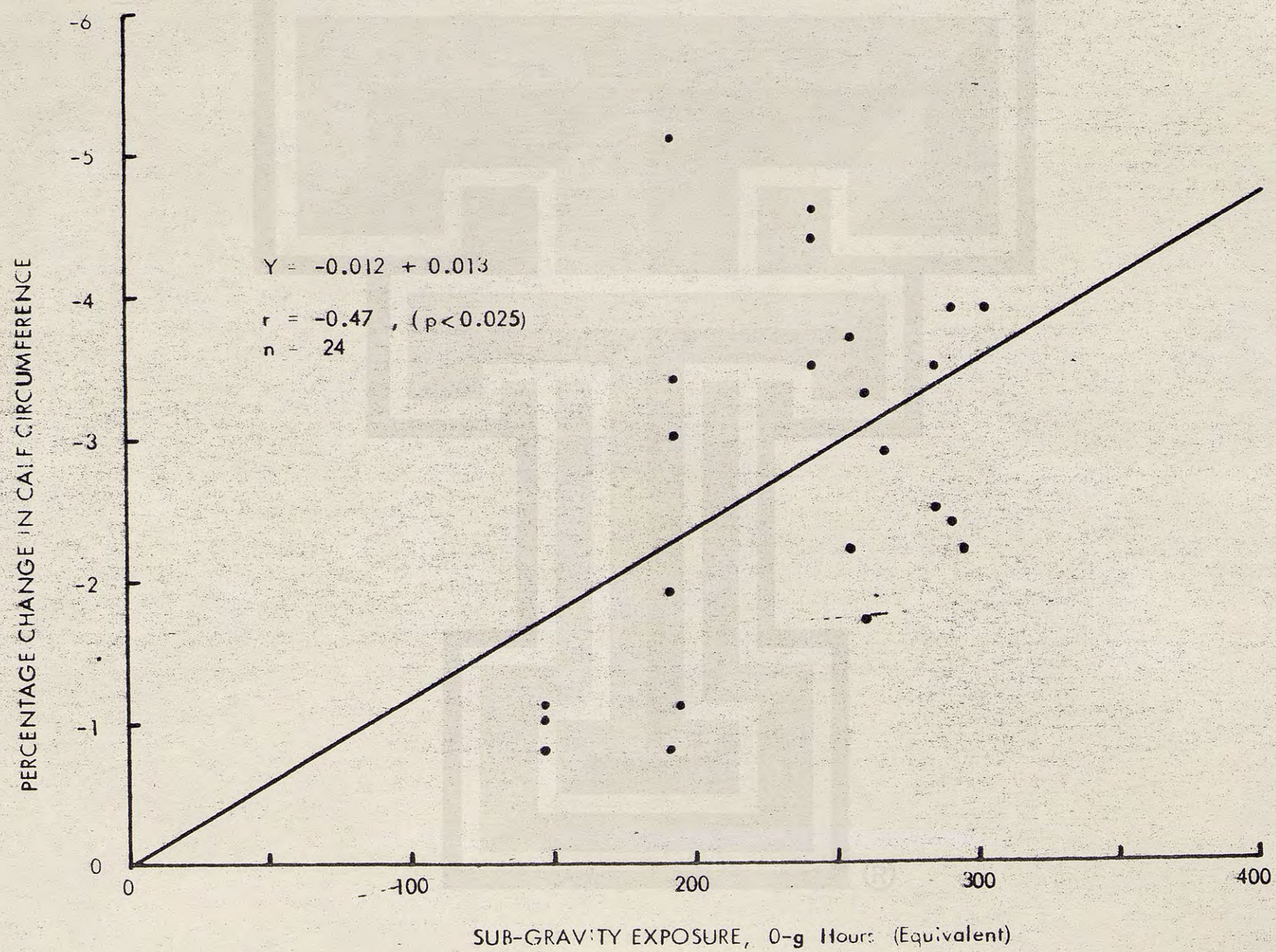
O INFLIGHT URINARY LOSS (INDIRECT MEASUREMENT OF
MUSCLE MASS)

- NITROGEN BALANCE
- PHOSPHORUS BALANCE

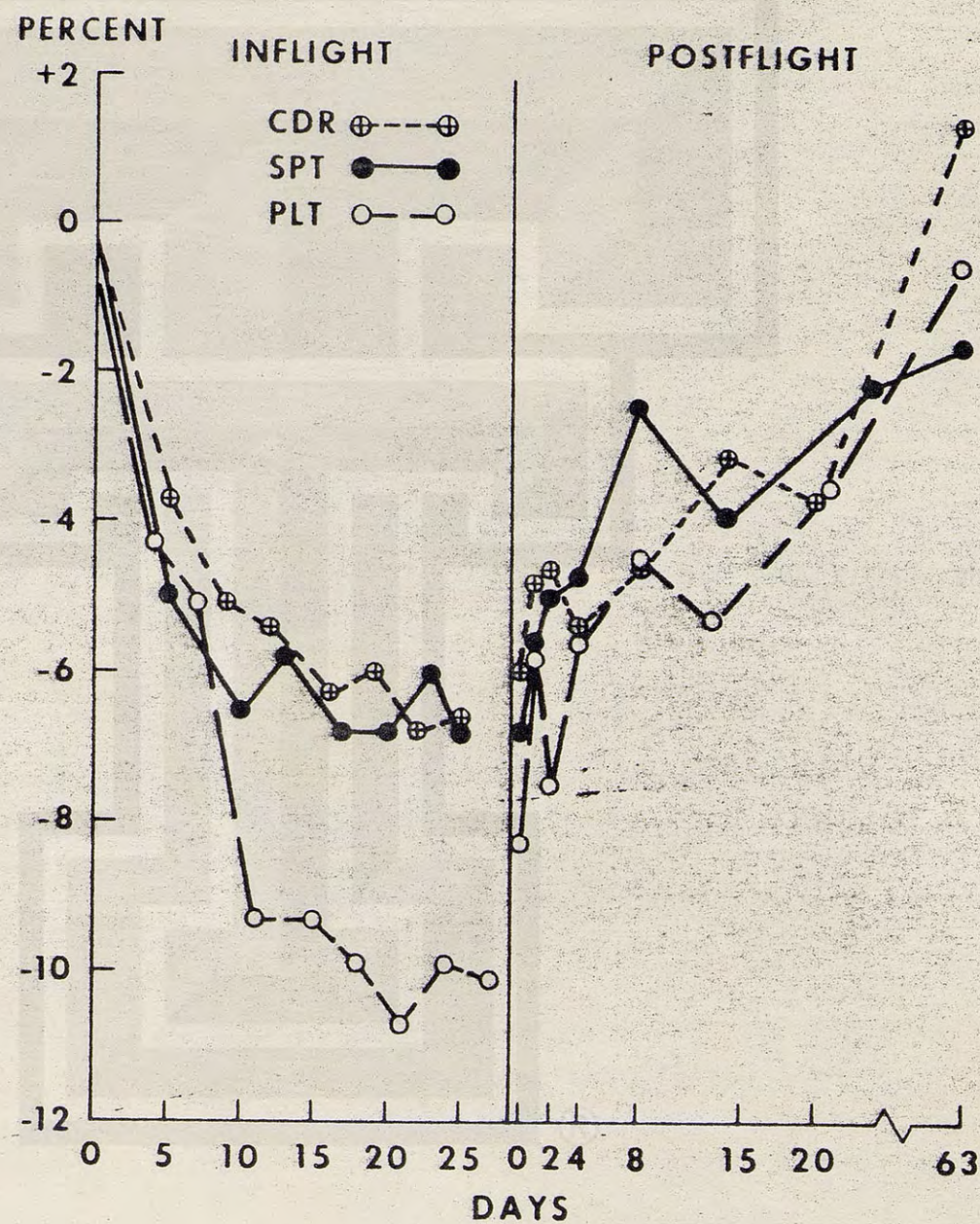
MANNED SPACE FLIGHT

- O DECREASE IN POST FLIGHT CALF GIRTH AND BODY WEIGHT OBSERVED DURING GEMINI MISSIONS
- O DECREASE IN POST FLIGHT CALF GIRTH AND BODY WEIGHT DOCUMENTED DURING THE APOLLO MISSIONS
- O DATA OBTAINED FROM SKYLAB MISSIONS SHOWED
 - DECREASED BODY WEIGHT
 - DECREASED INFLIGHT AND POST FLIGHT LEG VOLUMES AND CALF GIRTHS
 - INCREASED ELECTRICAL ACTIVITY OF ANTIGRAVITY MUSCLES
 - DECREASED MUSCLE COORDINATION
 - DECREASED LOWER EXTREMITIES MUSCLE CONTRACTILE FORCE
 - INCREASED INFLIGHT URINARY EXCRETION OF NITROGEN AND PHOSPHORUS
- O DATA OBTAINED FROM SOVIET FLIGHTS IS SUGGESTIVE IN ANTIGRAVITY MUSCLE DEGENERATION
- O BED REST FINDINGS SUPPORT THE ABOVE DATA

APOLLO MISSIONS

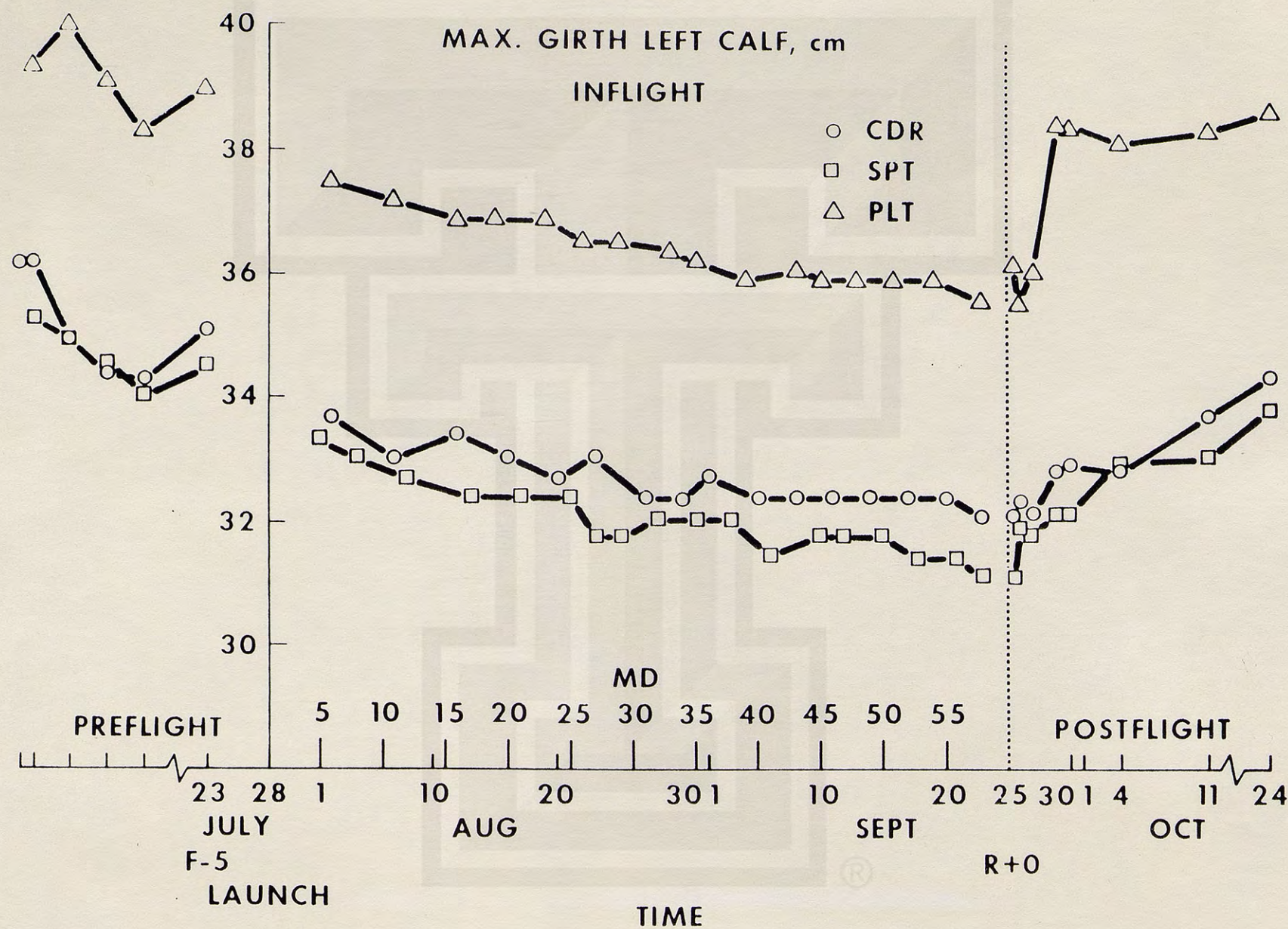


SL2 RESTING CALF
CIRCUMFERENCE
(MEAN OF R + L) -
CHANGE FROM
PREFLIGHT

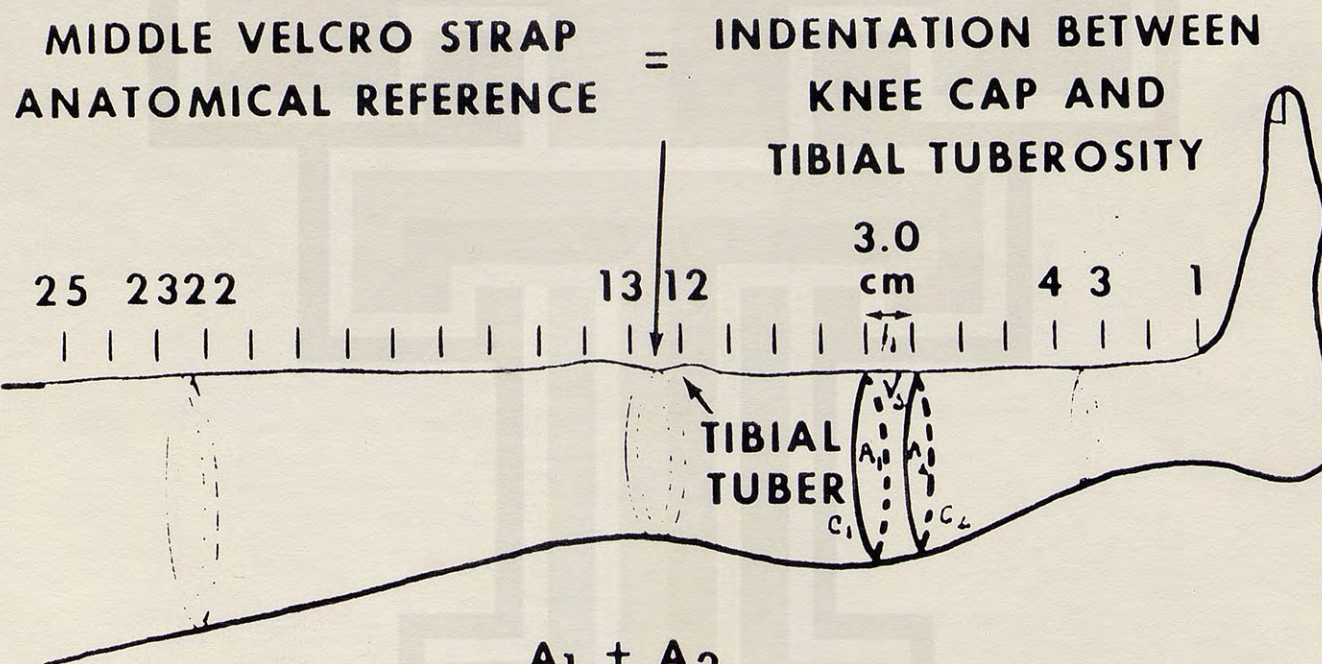


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SL 3



LEG VOLUME MEASUREMENT BY CIRCULAR CONE SEGMENTS

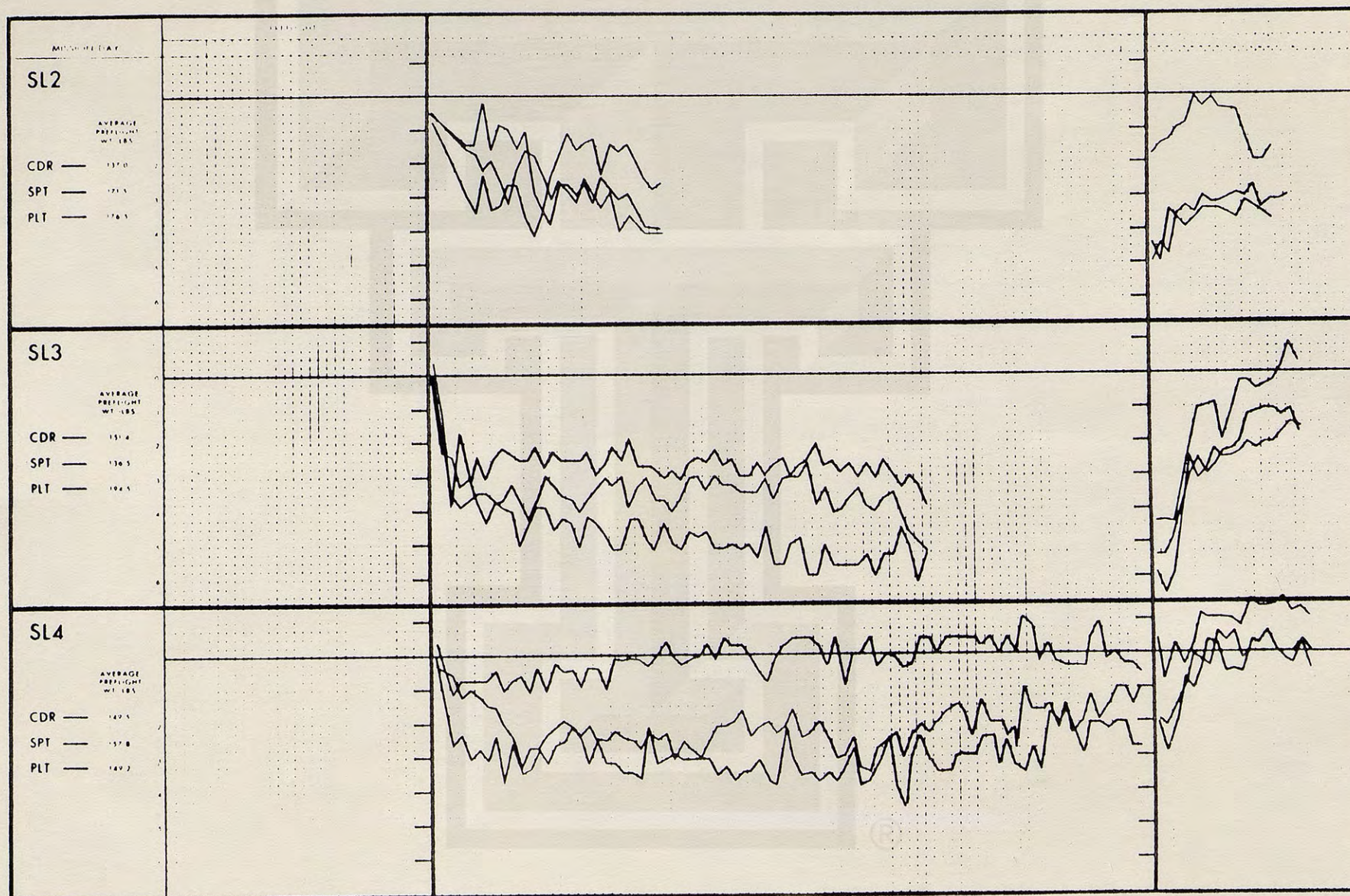


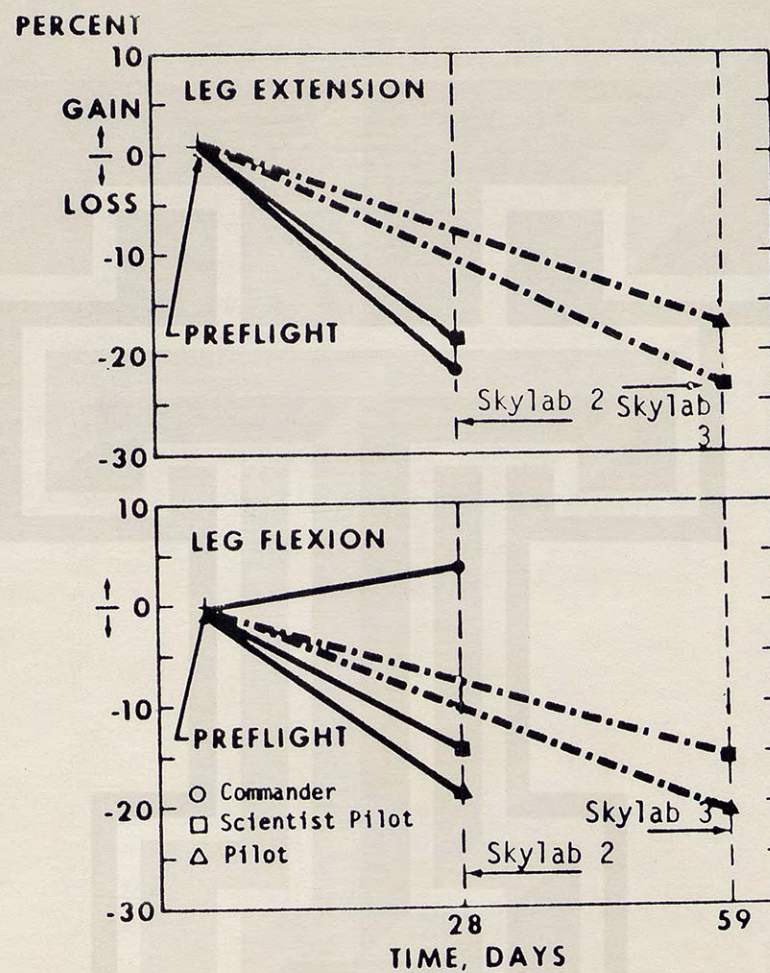
$$V_c = \frac{A_1 + A_2}{2} \cdot h$$

$$= \left[C_1^2 + C_2^2 \right] \cdot \frac{h}{8\pi}$$

- A = CIRCULAR AREA
- C = CIRCUMFERENCE
- h = HEIGHT = 3.0cm
- V_c = CIRCULAR CONE VOLUME

HEALTH TREND - BODYWEIGHT CHANGE FROM PREFLIGHT AVERAGE

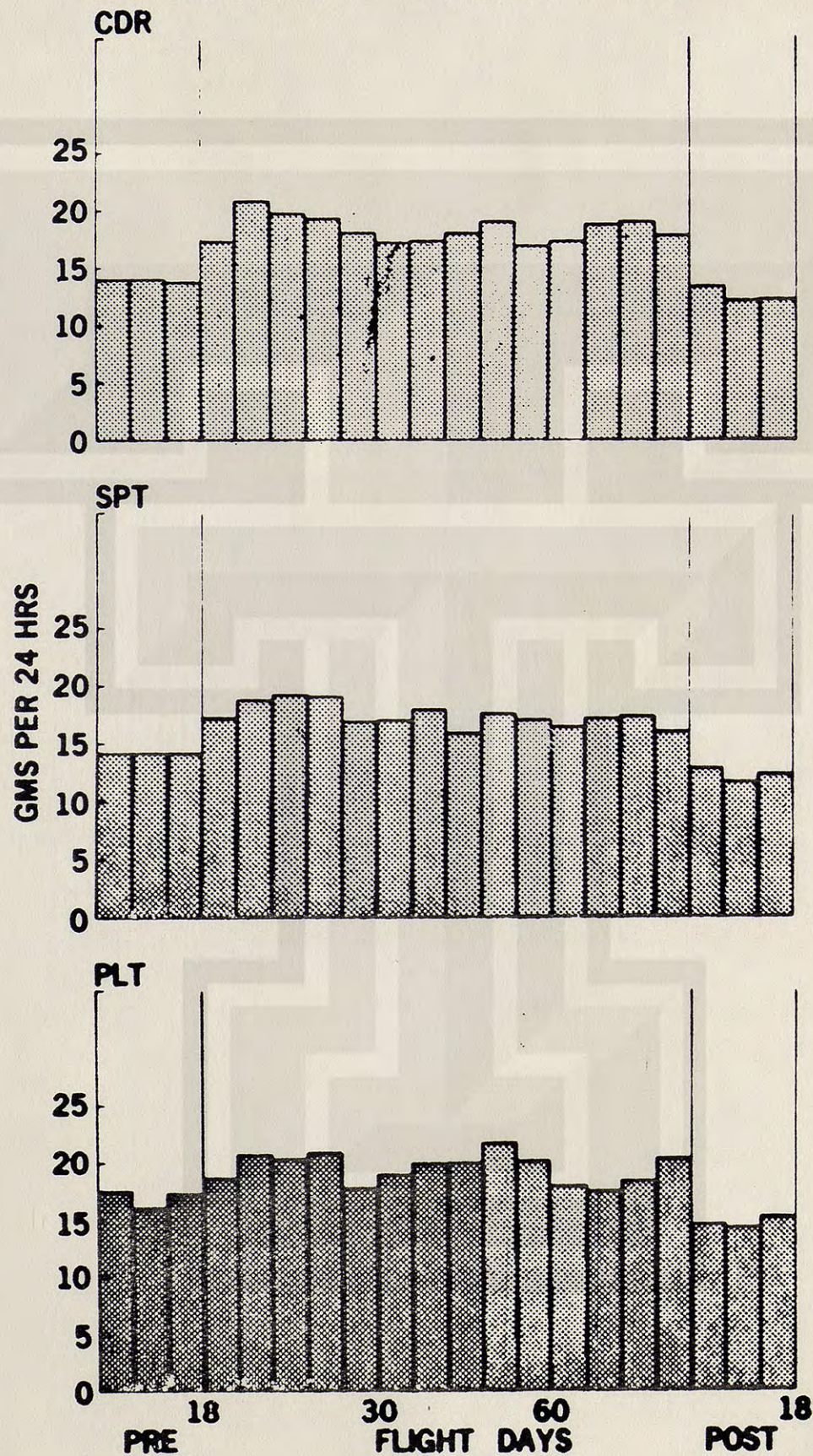




Changes in leg forces on Skylab 2 and Skylab 3.

URINARY NITROGEN, SKYLAB-4

NASA
S - 77 - 21719



NITROGEN BALANCE Skylab vs. Immobilized Bed Rest (gm/day)

	<u>Ambul.</u> <u>Control</u>	<u>In-flight</u> <u>(bed rest)</u>	<u>Shift</u>
SL-2,3 (mean, 6 astros)	+3.7	-0.8	-4.5
Immobil. (mean, 4 subjs)	+1.2	0	-1.2

SIGNIFICANCE FOR SHUTTLE

O ON THE BASIS OF PREVIOUS EXPERIMENTS:

- NO SIGNIFICANT PROBLEMS ARE ANTICIPATED WITH MISSIONS OF UP TO 30 DAYS DURATION
- SELECT PAYLOAD SPECIALISTS FREE OF BONE AND CALCIUM METABOLISM DISORDERS
- PROVIDE ADEQUATE MINERAL DIET AND PHYSICAL EXERCISE (ESPECIALLY LOWER EXTREMITIES)

O FOR MISSIONS OF LONGER DURATIONS DEVELOP ADEQUATE
COUNTER MEASURES

MUSCULOSKELETAL SYSTEM

O FINDING

O MODERATE LOSSES OF CALCIUM, NITROGEN, AND PHOSPHORUS

O POSSIBLE ETIOLOGICAL FACTORS

O PRIMARY LOSS OF GRAVITY GRADIENT

O SECONDARY

- ABSENCE OF WEIGHT BEARING
- ABSENCE OF HYDROSTATIC VENOUS GRADIENT
- ?HORMONAL IMBALANCE (ELEVATED CORTISOL SECRETION)
- COMBINATIONS OF ABOVE

O CANDIDATE FUTURE STUDIES

O ABSOLUTE CATABOLIC IN-FLIGHT CHANGES (BONE, MUSCLES)
IN ANIMALS

O COUNTERMEASURE EVALUATION

- DIETARY
- PHYSICAL
- ?HORMONAL

O SELECTION CRITERIA FOR PROLONGED MISSIONS
(PREDICTION FORMULA)

FUTURE RESEARCH EFFORT

BONE & MUSCLE ALTERATIONS

A. MECHANISMS OF MUSCULOSKELETAL CHANGES

1 - BONE

2 - MUSCLE

B. AMPLIFY INTERPRETATION OF SKYLAB DATA (GROUND BASED CORRELATIVE DATA)

C. DEVELOP PREDICTIVE INDICES OF SUSCEPTIBILITY TO MUSCULOSKELETAL DETERIORATION (SELECTION)

1 - BONE

2 - MUSCLE

D. DEVELOP IN-FLIGHT CAPABILITY FOR PREDICTING SKELETAL CHANGE RATES

E. MUSCULOSKELETAL COUNTERMEASURES

1 - BONE

2 - MUSCLE

F. BIOINSTRUMENTATION AND METHODOLOGY ADVANCEMENTS

1 - BONE

2 - MUSCLE

G. PREPARATION OF FLIGHT EXPERIMENTS

BONE CHANGES IN SPACE FLIGHT; PHYSIOLOGY OF THE PROBLEM.....DR. S. P. VINOGRAD,
Director, Bioresearch
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- VI. EXAMPLE BONE DISEASES

Fig. 1

I. BONE COMPOSITION

MATRIX

COLLAGEN FIBERS

GROUND SUBSTANCE

CALCIUM SALTS

HYDROXYAPATITE XTALS (Ca , PO_4 & OH)

ADSORBED CALCIUM SALTS (EXCHANGABLE Ca) AND OTHER IONS

(BINDING AND NODULAR ARRANGEMENT → STRENGTH & FLEXIBILITY)

Fig. 2

II. BONE FORMATION

OSTEOBLASTS SECRETE MATRIX (CARTILAGE)

HYDROXYAPATITE XTALS PPT, WITHIN & AROUND
COLLAGEN FIBERS

GROUND SUBSTANCE ABSORBED (MOST OF IT)

III. DEPOSITION AND ABSORPTION OF BONE - A CONTINUAL PROCESS

OSTEOBLASTS → BONE DEPOSITION

OSTEOCLASTS → BONE ABSORPTION

NORMALLY, RATES ARE EQUAL THOUGH ACTIVITIES OF
EACH NOT IN THE SAME PLACE AND TIME

ADVANTAGES TO CONTINUAL PROCESS:

REPLACEMENT OF BRITTLE OLD BONE (MATRIX DEGENERATION)

REMODELING TO ADAPT TO ALTERED STRESSES

- ALTERED LINES OF FORCE

- ALTERED MAGNITUDES OF FORCE

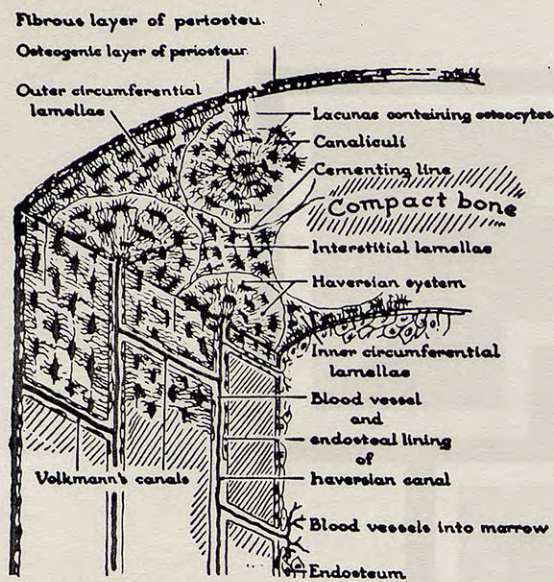


FIG. 160. A three-dimensional diagram showing the appearance of both a cross section and a longitudinal section of the shaft of a mature long bone. This diagram shows the relationship between the blood vessels of the periosteum, Volkmann's canals, Haversian canals and the marrow cavity.

Fig. 5

How Haversian systems can be added to older shafts

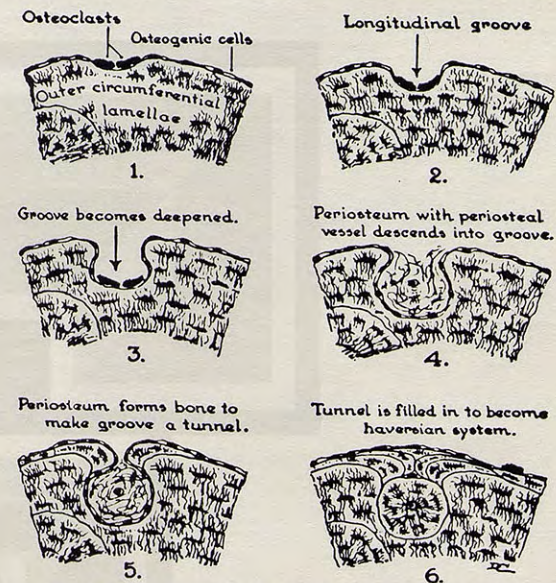


FIG. 158. Diagrams of cross sections of the shaft of a bone showing how Haversian systems are laid down under the periosteum in older bones to replace outer circumferential lamellae.

Fig. 6

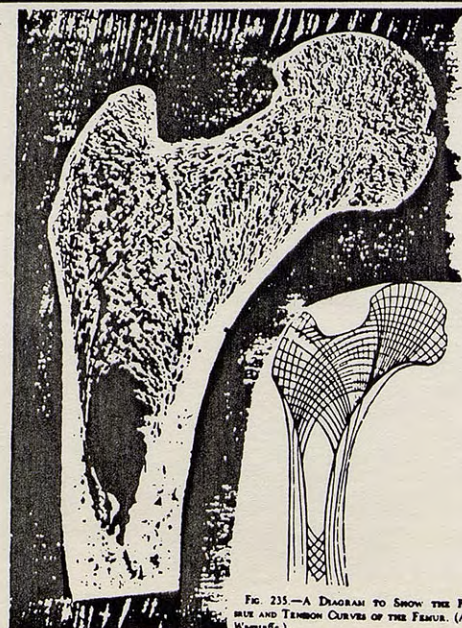


FIG. 235.—A DIAGRAM TO SHOW THE PRESSURE AND TENSION CURVES OF THE FEMUR. (After Wagstaff.)

327. Right thigh bone, femur, upper extremity, ground frontal section, from in front.

Fig. 7

III. DEPOSITION AND ABSORPTION OF BONE - (Cont'd)

RATES OF DEPOSITION & ABSORPTION:

FASTER IN YOUNG; SLOWER IN OLD

DEPOSITION > ABSORPTION WITH GROWTH, INCREASED BONE STRESS

ABSORPTION > DEPOSITION WITH DECREASED BONE STRESS (WTL., PHYSICAL INACTIVITY), ABNORMAL ALTERATIONS OF REGULATING FACTORS

BONE RESPONSE TO STRESS:

COMPRESSION → PIEZOELECTRIC EFFECT →
NEGATIVE POTENTIAL AT SITE OF COMPRESSION
→ SMALL ELECT. CURRENT → OSTEOBLASTIC STIMULATION AT NEGATIVE END

Fig. 8

III. DEPOSITION AND ABSORPTION OF BONE - (Cont'd)

LACK OF COMPRESSION (OR DECREASE) →
 DECREASED OSTEOBLASTIC ACTIVITY;
 OSTEOCLASTIC ACTIVITY CONTINUES AT NORMAL
 RATE → NET BONE ABSORPTION

BONE IS A LIVING TISSUE - MAINTAINED BY AND
 RESPONSIVE TO ACTIVITY; ATROPHYING WITH
 DISUSE.

Fig. 9

IV. CALCIUM AND PHOSPHATE METABOLISM

SOURCES
 GI ABSORPTION
 GI SECRETION
 GI EXCRETION
 URINARY EXCRETION
 BODY DISTRIBUTION
 LEVELS IN BLOOD AND ECF
 HYPOCALCEMIA
 HYPERCALCEMIA

Fig. 10

V. REGULATING FACTORS

- EXCHANGEABLE CALCIUM (minutes to hours)
 PRIMARY SOURCE: ADSORBED Ca SALTS IN BONE
- PARATHYROID HORMONE (hours to days)
 FROM PARATHYROID GLANDS
 STIMULATED BY DECREASED EC Ca LEVELS; INHIBITED
 BY ELEVATED EC Ca
 ACTS TO INCREASE EC Ca:
 INCREASES OSTEOCLAST ACTIVITY (& NUMBERS)
 DECREASES URINARY OUTPUT OF Ca (INCREASES URINARY
 OUTPUT OF PO_4)
 INCREASES GI ABSORPTION OF Ca
 HIGHLY DEVELOPED HOMEOSTATIC MECHANISM; NARROW EC Ca
 RANGE MAINTAINED; GLAND SIZE REFLECTS CHRONIC
 ACTIVITY STATE, i.e., ATROPHY WITH BONE DISUSE
- VITAMIN D (D_2 & D_3)
 ESSENTIAL FOR ABSORPTION OF Ca FROM GUT
 GENERALLY, SAME EFFECTS AS PTH, BUT GREATER ON Ca
 ABSORPTION; LESS ON BONE RESORPTION
 ABSENCE GREATLY IMPAIRS PTH ACTION ON BONE RESORPTION

V. REGULATING FACTORS (cont.)

- CALCITONIN (minutes)
 FROM THYROID GLAND IN HUMANS (THYROCALCITONIN)
 STIMULATED BY ELEVATIONS OF EC Ca; INHIBITED BY
 LOW EC Ca
 ACTS TO SHARPLY INHIBIT BONE ABSORPTION
 CAUSES DECREASE OF EC Ca
 ANTAGONISTIC TO PTH
 AS REGULATOR OF EC Ca:
 ACTION OPPOSITE TO PTH
 ACTION MUCH FASTER THAN PTH
 ACTS AS A SHORT TERM REGULATOR - UNLIKE CHRONICALLY
 DOMINANT PTH SYSTEM

VI. EXAMPLE BONE DISEASES

OSTEITIS FIBROSA CYSTICA - PTH XS

RICKETS - VITAMIN D INSUFF.

OSTEOMALACIA - ADULT RICKETS

OSTEOPOROSIS - DISUSE, etc.