THE CALCIUM METABOLISM PROBLEM IN SPACE MEDICAL SCIENCE

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Abstract. The currently frustrating problem of discrepancies between the non-significant calcium metabolic balance reports and the radiologic indications of bone loss in astronauts is discussed in reference to clinical data derived from human subjects with their musculoskeletal system immobilized by plaster casts.

The pertinent literature is cited, the biochemical profile of environmentally induced osteoporosis is presented, the various concepts of calcium metabolism are reviewed, the clinical chemistry with radiologic findings on the Gemini astronauts are discussed, and the weightlessness syndrome is related to calcium utilization in the body.

Hormones are assessed as relatively active in calcium absorption, in bone resorption, and in accelerating metabolic activity. Enzymes are portayed as behaving somewhat passive in calcium metabolism disorders.

It is concluded that the results of research now in progress may clear up the problem of whether the densitometric results are in error or whether there occur intra-skeletal transfers of bone mineral not detected by balance investigations.

Currently the most frustrating problem in space medicine and space biochemistry is the marked discrepancy between calcium balance findings and densitometric results obtained on astronauts. The body content of calcium exceeds that of all other minerals, approximately 2% of the body weight. Nearly all of this is in the bones. The metabolism of calcium, an electrolyte, has been under surveillance for many years in an attempt to fully understand absorption of calcium, regulation of serum calcium, blood-bone equilibrium, relationships between concentrations of calcium and phosphate ions, the resorption phenomena, and the calcium-calcitonin physiology. In Figure 1 main oral pathways and other known calcium ion pathways are shown. Although little has been published to date and essentially no experience has been gained to date in the branches of space clinical medicine, sharp focus has already been directed toward understanding why radiologists can demonstrate distinct bone losses and biochemists can point out no bone loss.

Specific literature on this subject was analyzed from the space clinical medical aspect by Busby (1968), Lynch *et al.* (1967), Deitrich *et al.* (1948), Lutwak *et al.* (1969), Mack (1965), Mack *et al.* (1967), and particularly, Neuman (1969). From the aspect of calcium deficiency and nutrition, reports were analyzed by Nordin (1960) and Vanderveen (1969), from the standpoint of weightlessness inducing losses of skeletal mass by Whedon (1960), Howard *et al.* (1945), and Deitrich *et al.* (1948), from the physiology aspect by recent reports (Busby, 1968; Deitrich *et al.*, 1948; Fourman, 1960; McLean and Urist, 1961; Poortman, 1969; Rodahl *et al.*, 1960), from the endocrino-

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logic side by Talmage and Elliott (1958), and from the general aspects pertinent to this problem, certain reports were selected (Bold, 1969; Douglas, 1963; Feldman, 1969; Imshenetsky *et al.*, 1969; McLean and Urist, 1961; Rodahl *et al.*, 1960; Urist *et al.*, 1962). Emphasis herein is on astronaut subjects and subjects exposed to an environmentally induced osteoporosis condition, such as volunteer airmen placed in a diminished atmospheric pressure chamber, and reference clinical material derived from polio-patients, paraplegics, arthritic patients, and fracture patients.

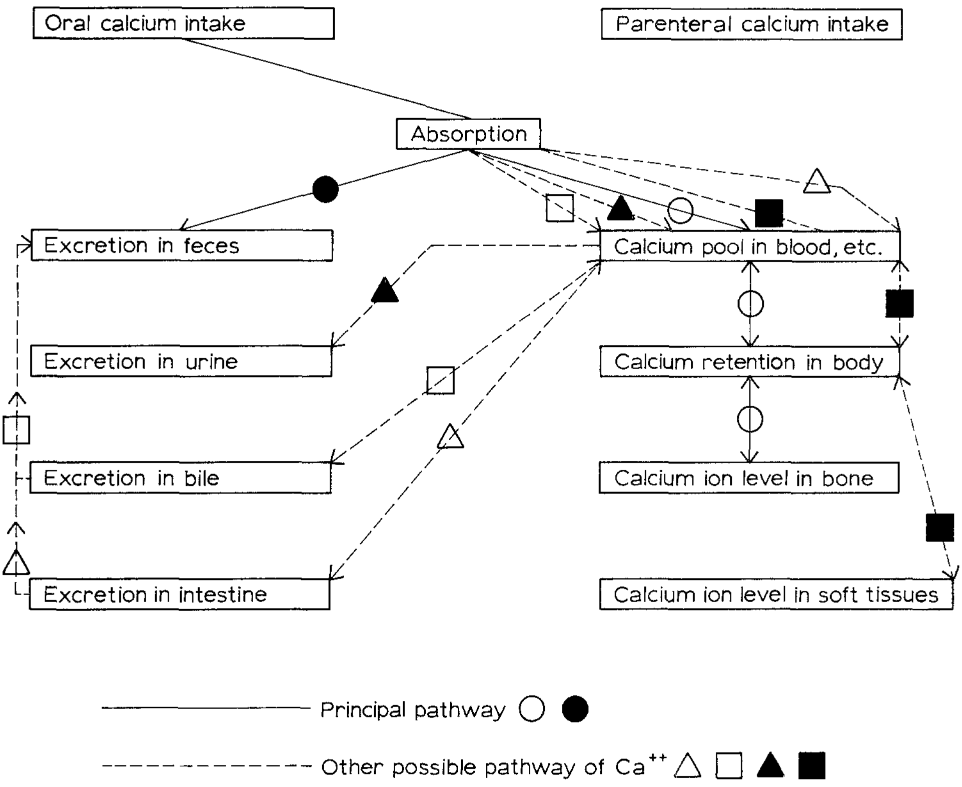

Fig. 1. Main calcium pathways.

Clinical measurements using atomic absorption spectroscopy with internal standardization to increase the precision and accuracy of total serum calcium and calcium activity (Feldman, 1969) coupled with Bold's automated method for estimating the diffusible fraction of calcium in plasma (Bold, 1969), improve the methodology for studying the calcium metabolism. With such measurements of dialysable calcium, more information may be forthcoming on the regulation of serum calcium. Preferred analytical procedures for calcium are atomic absorption spectrometry and flame photometry, with less dependability placed on EDTA systems (Douglas, 1965). Balance studies (Deitrich *et al.*, 1948) carried out in the past and the results of Gemini

VII balance studies (Lutwak *et al.*, 1969; Neuman, 1969) and the calcium intake evaluations for space flight carried out by Vanderveen (1969), all have attested the value of atomic absorption and emission spectrometry in analyzing calcium, magnesium, sodium and potassium.

In osteoporosis, the plasma calcium, phosphorus and alkaline phosphatase levels are usually in the normal range, with a considerable increase of the urinary calcium output during the early stage of osteoporosis. Total plasma calcium should maintain a normal level of 2.5 m mol/liter in accordance with the new terminology (Dybkær and Jørgensen, 1967). The hydrolase, alkaline phosphatase, 3.1.3.1 (Florkin and Stotz, 1964), expressed as *U*/liter activity (Dybkær and Jørgensen, 1967) should not be significant, although future investigations of enzymes may be of value, such as glucose-phosphate isomerase (5.3.1.9) and glucose-6-phosphate dehydrogenase (1.1.1.49) among others (Douglas, 1963).

If the rate of bone loss exceeds that of formation of new bone, the roentgen shadow cast by the bone will be less dense than normal and there will be a condition of skeletal rarefaction. There is no histological evidence that calcium nor calcium salts are being removed from the bone leaving the matrix behind.

The concentration of calcium in the plasma may be regarded as a resultant of three influences: the absorption of calcium in the intestine, the excretion of calcium in the urine and feces, and the exchanges with calcium in the bones. In many conditions the skeleton apparently acts as a reserve of calcium and phosphorus, and if the plasma level of either is reduced, mobilization of calcium and phosphorus from the bones takes place.

Immobilization has been repeatedly shown to bring about a loss of skeletal substance accompanied by hypercalcemia, hypercalcuria, and a negative calcium balance. The predicted space-flight syndrome is an environmentally induced osteoporosis (Neuman, 1969). The cause of osteoporosis is not known (Urist *et al.*, 1962). One of the existing calcium metabolism problems is to evaluate the real relationship between hypercalcemia or hypercalcuria on one side and renal damage with possible calculi formation on the other. Much ground experimentation has been laid by Busby (1968) and Neuman (1969). It is unknown, however, what threshold concentration of calcium in either serum or urine exists below which the kidney is free from possible harm. Data adequate to settle this point are not available. The problem here is that serum calcium is so well regulated physiologically that drastic experimental manipulations, such as vitamin D intoxication, are required to produce chronic hypercalcemia.

Hypercalcemia has a marked effect on renal function and produces a polyuria. There was a significant polyuria in the Glenn flight and the National Aeronautics and Space Administration (U.S.A.) reported in 1962 that Carpenter voided a dilute urine at the same time he was undergoing hemoconcentration from excessive perspiring. Immobilized patients usually show only a mild polyuria. In reviewing available clinical laboratory evidence from pre-flight, in-flight, and post-flight data on both U.S.A. and U.S.S.R. astronauts, which incidentally follow a similar pattern, excretions of over

200 ml excesses per day were noted along with average serum calcium levels. Fourman (1960) reports that distinct high calcium levels in the serum are necessary to produce a marked polyuria.

The osteoporosis of immobilization is also attributed commonly to the reduced activity of the osteoblasts in the absence of normal stresses and strains, but the serum alkaline phosphatase which is supposed to reflect osteoblastic activity, is normal. Nordin (1960) states that the development of hypercalcemia in this condition suggests rather that bone is being destroyed than that it is not being formed, and this is the implication gained from animal studies. Nordin has also shown that solubility of bone powder is closely related to pH, and one wonders if circulatory stasis could not lead to a fall in pH in an immobilized limb and so to removal of calcium.

The slowness of onset of changes in calcium metabolism seem remarkable in immobilized normal patients. Moreover, the changes reported in literature to date were progressive serum calcium levels reaching maximum near the end of, or even after, the immobilization period had ceased which was an average of 6.5 weeks.

Lynch *et al.* (1967) has performed metabolic studies on healthy men before and during bed rest at ground level or at simulated altitudes and reported depressed bone resorption may represent another facet of altitude acclimatization.

New information has been shed on these calcium problems with the improved methodology for bone densitometry (Mack, 1965) and the test of Gemini astronauts (Mack *et al.*, 1967), plus the metabolic balance studies on the command pilot and pilot of Gemini VII before, during and after the 14-day mission (Lutwak *et al.*, 1969). Employing scanning techniques and carefully controlling the film development with internal standards, Mack and her associates (Mack *et al.*, 1967) have greatly improved the reproducibility of densitometric measurements. Looking at this technique with balance studies performed on normal subjects, confirmation of negative calcium balances and bone loss as indicated by densitometry were observed in every case. Neuman (1969) has shown an inverse relationship between calcium intake and bone loss. In no instances in the Gemini V pilot examinations did the bone loss correlate with the duration of the flight and the magnitude of the changes were unbelievably alarming. If the lowest of the values was representative of the skeleton as a whole, the astronauts were losing calcium at a rate of over 10 grams per day. A consistent pattern was observed in the data on balances of potassium, sulfur, phosphate and nitrogen.

Possibly an assumption that bone undergoes partial reabsorption in the weightless environment leads to the thought that the resulting excessive excretion of the products of bone reabsorption might be conducive to urinary calcium formation. This makes it necessary to consider urinary calculus a potential clinical medical problem of prolonged space missions. The most comprehensive description to date is by Busby (1968) who presents the known clinical manifestations, diagnosis, prevention, and treatment of urinary calculus.

None of the astronauts have experienced disorders or changes in renal function that would be referrable to a massive mobilization of skeletal calcium accompanied by hypercalcemia and hypercalcuria.

Biochemically confusing, the data on bone loss and calcium metabolism under space flight considerations have certain variables that should increase the mobilization of bone calcium, such as elevated oxygen tension, general inactivity, and lack of gravity. Other factors should reduce bone loss, such as low cabin pressure, adequate calcium intake, and isometric exercises (Mack *et al.*, 1967; Poortman, 1969). The densitometric changes in Gemini V were marked, but in Gemini VII they were minimal. Among the differences in the two flights, three may be important: duration, calcium intake, and exercise. The dietary calcium level was higher in Gemini VII and a program of isometric exercise, not carried out in Gemini V, was also included. Apparently these two variables overcame the effects of a longer flight duration.

Most noteworthy and disturbing is the marked discrepancy between the roentgen results and the balance findings. If we take the smallest bone losses in Gemini VII as indicative of the skeleton as a whole, we should have observed negative balances of over 2 grams of calcium per day! This was not observed. Either the densitometric results are in error or there are gross translocations of huge amounts of calcium within the skeleton that do not appear in the net totals of a balance study. It should be possible to settle this problem with further earth-based studies and moreover, there occur large shifts in protein balances and hormone excretion that should provide ample justification for a continuing study and an expansion of our metabolic knowledge of man as the adaptation to the ecological constraints of space flight for longer duration is underway.

Dr. Boris Yegorov reported no mineral metabolism data. His space ship had normal atmospheric pressure of ca. 760 mm with normal humidity, temperature and oxygen content. The U.S.A. space capsules use more oxygen in their atmosphere to offset the low pressure inside the cabin. The large quantity of oxygen may, however, entail the risk of influencing the human organism by increasing modifications in bone tissue in a weightless situation.

In the future, it might be possible to administer medication which will have an inhibiting effect on the bone reabsorption due to weightlessness. The drugs of current interest in this respect are derivatives of gonadal hormones (Whedon, 1960). It is noted that hormonal side-effects might be a problem with prolonged usage of such agents. Further research in this area is indicated, however.

There is little evidence of any endocrine control of calcium absorption. The adrenal cortical hormone and the thyroid hormone may increase the fecal loss of calcium. Calcitonin has been found to decrease the calcium level in the serum by inhibiting the release of calcium from the bones, which is caused by the continuous process of bone resorption. Normally this resorption should not exceed bone formation. Possibly in those conditions where it does, calcitonin, a polypeptide, might become a useful drug. Earlier opinions that the four small pea-sized endocrine glands, the parathyroids, manufactured and secreted parathormone and this hormone controlled calcium and phosphorus metabolism is somewhat questionable now. Maintenance of a normal plasma calcium level may depend on the activity of the parathyroids, nevertheless, which portray a feed-back mechanism role. Hypocalcemia apparently stimulates the parathyroid glands, which in turn promote mobilization of calcium from bone. Perhaps hypercalcemia inhibits the parathyroids. Talmage and Elliott (1958) and Rodahl *et al.* (1960) discuss these hormonal influences at great length.

Since the parathyroidectomized animal can mobilize calcium from its skeleton and can maintain the blood calcium, even though at a level much below normal, it seems likely that the hormone acts to increase the activity of a system already present. In this respect, it is analogous to the thyroid hormone, which is not essential for metabolic activity, but is required to step up the metabolism to its normal optimal level.

Reviewing the role that enzymes may have in the calcium problem, only one hydrolase has importance to date. Fourman stated a decade ago (Fourman, 1960) that plasma alkaline phosphatase is raised when a disorder of calcium metabolism leads to increased osteoblastic activity, in particular in hyperparathyroidism if the bones have become affected, and usually, though not always, in osteomalacia. In osteoporosis, the plasma alkaline phosphatase is normal, as mentioned earlier. Recent studies on the influence of diminished atmospheric pressure on enzymes measured on athletes exercising and compared to athletes exercising at normal atmospheric pressure show no detectable alkaline phosphatase changes (Poortman, 1969). Imshenetsky *et al.* (1969) studied numerous crystalline enzymes subjected to high vacuum for 72 hours and found the resistance varied considerably, although he found reduced activity of all enzymes tested except trypsin which bears no relationship to calcium metabolism. No true enzyme behavior at this time is related to the calcium metabolism problem, except the phosphatase.

Research on human subjects immobilized by plaster casts, including complete metabolic balance investigations, must eventually help in clearing up some of the problems. Ideal patients and normal controls should be without nervous dysfunction, but with musculoskeletal system immobilized.

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