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The Effects of Sodium Depletion on Bone Sodium Metabolism

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IT has been known for some years that bone mineral undergoes constant turnover throughout life (Shohl, 1939) and that bone is the only tissue in which the sodium concentration is higher than in extracellular fluid (Harrison *et al.*, 1936). However, it was not until the use of radioisotopes gave more accurate information about the dynamics of bone mineral metabolism that the potential importance of bone in sodium metabolism was appreciated (Hevesy, 1955; Neuman and Neuman, 1958).

Analysis of the whole human body, though limited to a few observations, has shown that the total sodium content is approximately 5,000 mEq. (Widdowson *et al.*, 1951; Forbes and Lewis, 1956). Of this total, probably not less than one-half is in bone. Ever since the earliest studies with radioactive sodium isotopes it has been realized that bone sodium does not exchange completely within periods adequate for complete exchange in all other tissues (Kaltreider *et al.*, 1941). Later work has repeatedly confirmed this observation in different species. For example, Bauer (1954) found in rats that only 30–40% of bone sodium exchanged with injected radiosodium within twenty-four hours and similar values have been reported in rabbits (Davies *et al.*, 1952), in dogs (Edelman *et al.*, 1954) and in man (Edelman *et al.*, 1952; Miller and Wilson, 1953; Miller *et al.*, 1954).

It is clear therefore that alterations in bone sodium metabolism may affect both sodium balance studies and the measurement of exchangeable sodium in man. It is known that loss of sodium from the body lowers bone sodium content (Bergstrom, 1955; Nichols and Nichols, 1956; Levitt *et al.*, 1956) and bone sodium content may rise after sodium loading (Nichols and Nichols, 1957) and after parathyroidectomy (Nichols and Nichols, 1958).

Until recently little was known about the effect of alterations of bone sodium content on bone sodium exchange. There are great difficulties in attempting to study alterations in bone sodium exchange in man during life. Using an external counting technique Miller *et al.* (1954) were able to obtain information about the penetration of radiosodium into bone in human subjects on a diet of low sodium content and in a steady state of sodium balance. Their method was not sufficiently sensitive to attempt to follow alterations under conditions of altering sodium balance. For this reason the effects of acute sodium depletion were studied in rats. In the first instance, it was established that the bone content of sodium increased with age, whilst the proportion available for exchange declined (Munro *et al.*, 1957). Thereafter the effects of acute sodium depletion were studied in groups of rats selected by weight. Sodium was removed from the body by peritoneal dialysis lasting four hours (Bergstrom and Wallace, 1954). On the morning of the next day the rats received an intraperitoneal injection of radiosodium and were killed twenty-four hours later. The whole procedure thus lasted forty-eight hours and the rats were fed on a diet of rice and distilled water throughout the experiment. Samples of blood and bone were obtained for measurement of radioactivity and sodium content.

It was confirmed that the procedure reduced the bone content of sodium. In rats of between 50 and 100 grams, for example, the bone sodium content of the depleted rats was 210 mEq./kg. dry bone, compared with 247 mEq./kg. dry bone in controls. In older animals the decrease in bone sodium was not so pronounced. Surprisingly, in both groups the amount of sodium available for exchange with the injected radiosodium was not altered. It is evident that the transfer of sodium from bone to extracellular fluid must in the first instance be from the exchangeable fraction which, by definition, is able to participate in ionic exchange with the extracellular fluid. These results suggest therefore that, after depletion, some sodium in bone which was not originally available for exchange had become exchangeable so that the absolute amount available remained constant. In the younger animals, the serum sodium level did

not fall after sodium depletion but in older animals which released sodium from bone less readily the serum sodium fell from 149 to 139 mEq./l.

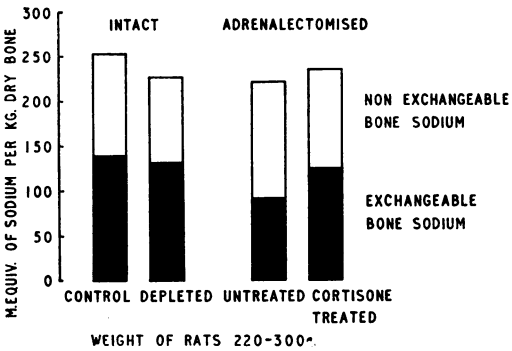

FIG. 1.—The effect of sodium depletion on bone sodium metabolism in intact and adrenalectomized rats.

Because of the known importance of the adrenal glands in sodium metabolism, attention was next directed towards the effect of adrenalectomy on bone sodium. In contrast to the normal renal sodium conservation of intact animals, adrenalectomized rats (220–300 grams) fed on a diet of low sodium content continued to excrete sodium in their urine. Within forty-eight hours the bone sodium content rapidly declined from 256 to 222 mEq./kg. dry bone and there was a slightly less abrupt fall in serum sodium level from 149 to 132 mEq./l.

The injection of radiosodium revealed that the drop in bone sodium content was associated, in these circumstances, with a reduction in the exchangeable fraction. At the time of death sodium intake had been restricted for seventy-two hours and the animals felt cold and limp. When treated with cortisone acetate during the period of sodium restriction, however, their general condition was improved and though bone sodium did fall, the effect on exchange was much less striking, so that the alterations corresponded more closely to the effects of sodium depletion in intact animals (Fig. 1). The changes could be completely avoided by the simultaneous administration of cortisone and saline. A possible explanation for the decreased exchange in untreated, adrenalectomized rats is that the circulation was so impaired that the sodium isotope was not carried fully into the bone (Munro *et al.*, 1958).

The results of animal experiments cannot be assumed to be directly applicable to man. Nevertheless, there is a close resemblance between the structure of bone mineral in different species (Neuman and Neuman, 1958), and the bone sodium content and exchange in health are also similar. It is therefore highly probable that sodium depletion in man is associated with changes in bone sodium metabolism resembling those encountered in these experiments. Moreover, such changes provide a possible explanation for the discrepancies in balance studies which have been noted in earlier reports (Wilson and Miller, 1953; Atchley *et al.*, 1933; Flanagan *et al.*, 1950).

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