SOUTH AFRICAN MEDICAL JOURNAL SUID-AFRIKAANSE TYDSKRIF VIR GENEESKUNDE

Cape Town, 1 May 1965 Volume 39 No. 16 Deel 39 Kaapstad, 1 Mei 1965

EDITORIAL : VAN DIE REDAKSIE

THE DISORDER OF CALCIUM METABOLISM IN SARCOIDOSIS

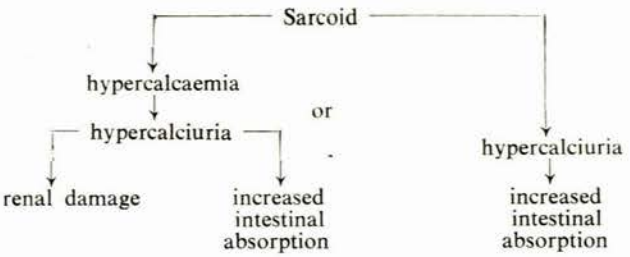
A raised level of serum calcium, hypercalciuria, renal stones, nephrocalcinosis and renal failure may be found in some patients suffering from sarcoidosis. Deposition of calcium may occur in the eye (particularly the cornea) and other soft tissues. The cause of this disturbance of calcium metabolism is apparently not secondary hyperparathyroidism, nor generalized destruction of bone, nor sarcoid of the kidneys, nor an excessive binding of calcium to protein in association with hyperglobulinaemia (which would not produce hypercalciuria). Albright and his group[1,2] and Dent and colleagues[3] independently showed that faecal calcium was so low in their patients with sarcoidosis and hypercalcaemia that, despite hypercalciuria, calcium balance did not become negative. Both these groups commented on the resemblance of this condition to hypervitaminosis D, and postulated either an overproduction of a calciferol-like substance or an unusual sensitivity to it. Cortisone or its analogues were shown to reduce both the hypercalcaemia and the hypercalciuria, and this led Dent to conclude that cortisone might be an antagonist of vitamin D. The idea of excessive sensitivity to vitamin D in some patients with sarcoid was not new, and the production of hypercalcaemia with small doses (e.g. 10,000 units a day), or with ultraviolet light, had been described by Scadding,[4] Larsson *et al.*,[5] Anderson *et al.*,[3] Cantwell[6] and Mather.[7]

In the belief that the toxic effects of excessive amounts of vitamin D were caused primarily by an over-absorption of calcium from the bowel, both Albright's and Dent's groups concluded that the primary defect in calcium metabolism in sarcoidosis was a similar intestinal over-absorption.

From the beginning, however, it was realized that over-absorption could not be the whole story since the *urinary excretion of calcium was often considerably greater than the total amount of ingested calcium*. Despite this glaring discrepancy the logical fallacy of primary over-absorption in sarcoid has been generally accepted, virtually without demur, and is quoted today in almost all places when the topic comes up, e.g. in a leading article in the *British Medical Journal*.[8]

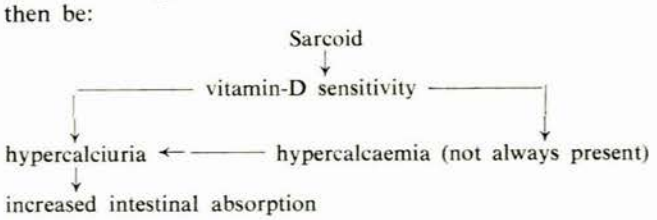
Jackson and Dancaster[9] investigated this problem in 1959 and found several other discrepancies in the theory that sarcoid led to over-absorption of calcium; this to hypercalcaemia; this to hypercalciuria and the deleterious effects on soft tissues. These discrepancies may be listed: (1) urine calcium often greater in amount than total ingested calcium; (2) hypercalciuria of severe degree (e.g. mean of 600 mg. per day in one case) may be present with sustained normocalcaemia; (3) on cortisone, a reduction in serum calcium level often occurs considerably before the reduction in urinary calcium excretion and *without change in faecal* calcium (i.e. without change in intestinal absorption); (4) on a very low calcium intake—that is when the gut cannot possibly over-absorb calcium since it has nothing to over-absorb—both the serum calcium level and the urinary calcium may remain elevated, even for months. Consequently it must be concluded that over-absorption could not possibly have been the responsible agent; but (5) conversely, a great increase in dietary calcium produces only very small changes in urinary calcium, whereas with an excessive absorptive capacity one would expect great increases in the calciuria.

It is clear then, that the following sequence of events cannot satisfactorily explain the calcium disorder in sarcoid: increased intestinal absorption of calcium → raised serum calcium level → hypercalciuria → renal damage. Jackson and Dancaster suggested a different relationship, whereby the primary effect of the sarcoid was to raise serum calcium (the extra calcium presumably coming from bone), or urine calcium (by a presumed direct effect on renal tubular handling of calcium). The hypercalciuria may itself then lead to a *compensatory intestinal over-absorption*, as follows:



They produce a good deal of evidence that this sequence of events may occur in other conditions, such as in the pharmacological state of vitamin-D overdosage.[9,10]

It is plain that hypersensitivity of vitamin D *could* explain these phenomena, especially since vitamin-D intoxication responds just as readily to cortisone as do the calcium upsets in sarcoidosis. The mechanisms might then be:



One difficulty in the hypothesis that vitamin-D sensitivity accounts for the calcium disturbances in sarcoidosis is that not all patients appear to be sensitive to fairly large doses. The great and rapidly occurring sensitivity in some other subjects suggests that there must be at least two groups of sarcoid patients with calcium disturbances—those who are sensitive to vitamin D, and those who are

not. Fortunately, the latter group also appear to respond well to adrenocortical steroids.

The hypothesis of intestinal compensation for high urinary calcium loss may be expected to apply to other conditions, in fact might be considered as a possible general physiological mechanism.[9,10] This relationship will not always hold (e.g. not in immobilization); but if it is looked for, perhaps it may be found with surprising frequency. Such a chain of events must normally be occurring all the time, since different normal adults may have consistently different urinary calcium outputs, ranging from 50 mg. in some cases to 400 mg. per day in others. These great individual variations of urinary calcium in normal adults, the relative constancy of urinary calcium excretion in each subject over long periods under normal conditions, and the extremely small changes produced in urinary calcium by great changes in calcium intake, have been fully attested on a large scale by Knapp,[11] Nicolaysen *et al.*,[12] and Hodgkinson and Pyrah.[13] Yet, whatever the natural level of urinary calcium may be, each normal adult maintains a net bodily balance for calcium when considered over long periods. Thus his intestinal absorption must be naturally compensating and attuning itself to the level of urinary loss. The absorptive calcium 'barrier' is therefore controlled by the urinary output.

However good or poor this general theory may turn out to be, it must surely be clear that over-absorption cannot be the primary lesion of calcium metabolism in sarcoidosis. We believe it to be a compensatory phenomenon.

1. Henneman, P. H., Carroll, E. L. and Dempsey, E. F. (1954): J. Clin Invest., **33**, 941.
2. Henneman, P. H., Dempsey, E. F., Carroll, E. L. and Albright, F. (1956): *Ibid.*, **35**, 1229.
3. Anderson, J., Harper, C., Dent, C. E. and Philpot, G. R. (1954): Lancet, **2**, 720.
4. Scadding, J. G. (1950): Brit. Med. J., **1**, 745.
5. Larsson, L. G., Liljestrand, A. and Wahlund, H. (1952): Acta med. scand., **143**, 280.
6. Cantwell, D. F. (1954): Irish J. Med. Sci., **6**, 223.
7. Mather, G. (1957): Brit. Med. J., **1**, 248.
8. Leading article (1964): Brit. Med. J., **2**, 707.
9. Jackson, W. P. U. and Dancaster, C. P. (1959): J. Clin. Endocr., **19**, 658.
10. *Idem* (1961): *Ibid.*, **22**, 195.
11. Knapp, E. L. (1947): J. Clin. Invest., **26**, 182.
12. Nicolaysen, R., Eeg-Larsen, N. and Malm, O. J. (1953): Physiol. Rev., **33**, 424.
13. Hodgkinson, A. and Pyrah, L. (1958): Brit. J. Surg., **46**, 10.