HYPERCALCAEMIA AND CANCER

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MANY cancer patients develop a raised plasma calcium at some time during the course of their illness. This has been emphasized by several workers including Swyer, Berger, Gordon and Laszlo (1950), Woodard (1953), Myers (1960), Warwick, Yendt and Olin (1961). Some cancers present with hypercalcaemia and cause considerable difficulty in differential diagnosis (David, Verner and Engel, 1962).

The symptoms of hypercalcaemia include lethargy, muscular weakness and hypotonia, anorexia, nausea, vomiting, constipation, dry mouth, thirst, polyuria and a variety of mental changes. These symptoms, which may be the major source of invalidity in hypercalcaemic cancer patients, can usually be relieved by measures which include cortisone administration, ablative endocrine surgery, hormone therapy, radiotherapy and occasionally by surgical removal of the tumour.

Cancerous hypercalcaemia is usually associated with bony metastases and in such cases it is probably due to erosion of bone by actively growing tumour cells, but the mechanisms are not always clear. Morbid anatomists of the last century recognized that certain cancers (particularly of the breast, lung and kidneys) had a special tendency to metastasize to bone. When chemical analytical methods became available in the earlier years of this century, attention was focussed on the chemical changes associated with this bony invasion and in 1936 Gutman, Tyson and Gutman showed that hypercalcaemia occurred in multiple myeloma and neoplastic disease involving bone. Many other studies followed.

Calcium Metabolism

The three main sites of regulation of calcium and phosphorus metabolism, as at present understood, are the intestine which is the portal of entry, the bones which are the storehouse and the kidneys which provide the excretory channel. Although it varies a good deal, the daily intake of calcium is commonly about 1,000 mg., of which the net absorption is only 100 to 250 mg. Since normal adults are in calcium balance the urinary excretion is equal to the net absorption of 100 to 250 mg. per day; 99% of the total calcium in the body is stored in the skeleton, but bone is a dynamic tissue in

which continuous deposition and resorption is associated with a large daily turnover of calcium between bone and bloodstream.

Several reviews of calcium metabolism, including those of Dent (1956) and Watson (1960), have emphasized that the plasma calcium is one of the important body constants which is normally maintained within a relatively narrow range despite these large daily exchanges of calcium between bone and bloodstream and from intestine to bloodstream to kidney.

Two chief physiological devices which contribute to this are the parathyroid secretions and vitamin D. Probably the chief function of the parathyroid glands is to regulate the mobilization of calcium from bone to bloodstream in order to maintain a normal plasma calcium level, while the best known and probably the most important action of vitamin D is to promote gastro-intestinal absorption of calcium and this, too, plays an important role in keeping the plasma calcium normal.

Hypercalcaemia and Bony Secondaries

It is clear that in cancer patients with widespread osteolytic lesions hypercalcaemia could result from a disturbance of blood-bone equilibrium so that a gross excess of calcium passes from the bones into the bloodstream. Myeloma, leukaemia and the reticuloses involving bone could all behave similarly.

In 1948 Albright and Reifenstein wrote 'The most obvious and probably the correct explanation . . . of the hypercalcaemia . . . is that the metastatic lesions are dissolving bone salts into the bloodstream more rapidly than the kidney can clear the blood of excess calcium'. Subsequent studies have confirmed the validity of this concept, showing that such patients usually have minimal gastro-intestinal absorption but a high urinary calcium so that they are in negative calcium balance, the whole process being an expression of bony dissolution (Laszlo, Schulman, Bellin, Gottesman and Schilling, 1952, Pearson, West, Hollander and Escher, 1952, Skoog, Adams and MacDonald, 1962). These observations have been confirmed in our own laboratories. Pearson, West, Hollander and Treves, (1954) reiterated that hypercalcaemia appeared only when the renal excretory capacity for calcium was exceeded, this capacity being about 500 mg. per day when renal function was normal. Others have not always

found such a neat relationship (for example Baker, 1956) though it is generally agreed that the urinary calcium excretion is a useful measure of the progress or regression of bony metastases. Some observers have recently questioned this view (Gardner and Gordon, 1962).

Hypercalcaemia without Bony Secondaries

In other cancer cases hypercalcaemia is not associated with demonstrable bony metastases, such patients having no clinical or radiological evidence of bone disease and a normal alkaline phosphatase. Some of them eventually prove to have bony metastases, but in others no secondaries are found and it now seems clear that cancer cells can produce chemical substances which modify calcium and phosphorus metabolism and cause a raised plasma calcium without anatomical invasion of bone tissue by tumour cells.

Some sort of humoral mechanism was postulated as long ago as 1923 by Klemperer and again in 1948 by Albright and Reifenstein, who studied a patient with a hypernephroma and speculated that the tumour produced a 'parathyroid-hormone-like' substance which accounted for the chemical findings. Better evidence came in 1956 when Connor, Thomas and Howard described two patients in whom hypercalcaemia disappeared completely when the primary tumour was removed. In the same year Plimpton and Gellhorn published studies from 10 patients with malignant hypercalcaemia without any evidence of invasion of bone. There have since been further case reports which support the idea of a humoral substance (Schatten, Ship, Pieper and Bartter, 1958, Abouav, Berkowitz and Kolb, 1959, Alanis and Flanagan, 1959, Gold and Shnider, 1959, Lucas, 1960, Stone, Waterhouse and Terry, 1961, Loebel and Walkoff, 1962, Fry, 1962).

Theories of Humoral Action

The nature of the substance and its mode of action have been the subject of much speculation. It has been suggested that hypercalcaemia may be due to an abnormal substance which circulates in the bloodstream in combination with calcium and produces, in a sense, a spurious hypercalcaemia. In support of this view Marsh and Walser (1961) reported that the plasma ionised calcium was increased in only half their cases whereas the complexed calcium was often raised. This has not been our experience. Using the method of Rose (1957) we have found increases in both ionised and protein-bound fractions in all hypercalcaemic cancer patients tested and the complexed fraction has always been normal.

Another theory is that the substance may be parathyrotrophic and produce hypercalcaemia by

stimulating the parathyroid glands and this is supported by the histological appearance of parathyroid hyperplasia in a few reported cases although the parathyroids have usually been reported as normal. We have not yet found any morphological evidence of parathyroid hyperplasia in our cancer patients.

Other theories have postulated direct peripheral actions and have endeavoured to characterize a substance in terms of known behaviour as vitamin D-like or parathormone-like. Attempts to demonstrate such activity in tumour extracts have so far been unsuccessful. Dr. Cuthbertson performed vitamin D assays on the plasma of several of our patients with normal results. More indirect approaches have also been disappointing, indeed there is no complete or satisfactory balance study from such a patient in the literature. Undoubtedly one of the reasons for this is the difficulty of obtaining standard conditions of dietary intake in hypercalcaemic cancer patients, who are usually troubled by nausea or vomiting.

With the co-operation of the Radiotherapy Department at University College Hospital we have collected for prospective study a group of women with inoperable breast cancer who at the time of selection were clinically well and had no evidence of bony metastases, but who were otherwise unselected. This investigation is current and at the time of writing it includes 45 patients. None of these was hypercalcaemic initially but about one third of them had a urinary calcium excretion above 250 mg. per day and 20% had a pronounced hypercalciuria in excess of 300 mg. per day. These patients were selected in such a way as to minimize the incidence of bony metastases and it is likely that in some of them the hypercalciuria is due to a humoral mechanism of the kind which later causes hypercalcaemia. If so, some will later develop a high plasma calcium, but in the meantime it is possible to study them while they are well and suitable subjects for calcium and phosphorus balances.

Balances have been performed in five of these hypercalciuric patients. On a daily intake of about 1000 mg. four were in approximate calcium balance and absorbing too much calcium from the diet. In these cases the daily urinary calcium excretions were about 300 mg., 350 mg., 450 mg. and 470 mg. After a follow-up of up to two years in the longest cases none has yet developed hypercalcaemia and this long follow-up strengthens the view that they do not have bony secondaries.

This picture is consistent with the action of a vitamin D-like substance, but the results in the fifth patient were quite different. On a daily intake of about 900 mg. of calcium she was in

negative calcium balance of about 450 mg. per day with a faecal calcium almost equal to intake and a daily urinary calcium excretion between 450 mg. and 500 mg. This picture is very similar to that we have seen in hypercalcaemic patients with bony metastases, but after 21 months of close observation during which time the urinary calcium has been constantly in excess of 400 mg. per day there is still no evidence of bony secondaries clinically or radiologically and the plasma alkaline phosphatase is normal.

A consideration of the amount of calcium dissolved makes it increasingly unlikely that she has had osteolytic bony secondaries throughout this period for they would be expected by now to produce some local evidence, clinically or radiologically, of activity even though initially small and widespread. On the other hand the whole picture is fully consistent with a humoral action on bone. Furthermore at the time of writing her plasma total calcium and plasma ionised calcium have both risen to the extreme upper limit of normality, though she is well and free of complaints.

We consider that this patient has evidence of a humoral substance, almost certainly arising from cancer cells, which is modifying her calcium

and phosphorous metabolism without the cells having invaded bone tissue. It is possible, too, that the other patients have a different humoral substance and there may be more than one mechanism for the production of hypercalcaemia in cancer patients by humoral means.

Summary

(1) Hypercalcaemia, which is not uncommon in cancer patients, is usually associated with osteolytic secondaries in bone. In such cases it is usually due to erosion of bone by actively growing tumour cells and the mechanism is clear.

(2) Less commonly, hypercalcaemia results from humoral substances produced by tumour cells which do not invade bone tissue.

(3) The nature and behaviour of these substances are under investigation. There may be more than one humoral mechanism for the production of hypercalcaemia in cancer patients.

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