CALCIAL METABOLISM AND THE PARATHYROIDS

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The discovery of the control over calcium metabolism exerted by the parathyroids and by vitamin D has led to a renewal of interest in the subject. Calcium had been regarded as a very inert substance, as it is deposited in the largest amounts in normal tissues with a sluggish metabolism, or in any dead tissue which is not infected, but it is so large or so situated that it cannot be absorbed. The replacement of elastic tissues by calcareous material is a characteristic feature of growing old. But all the activities of calcium cannot be disposed of so summarily, for calcium salts are essential to the heart beat, and, indeed, if they were simply inert, no bad results would follow their removal from the diet, which we know is not the case.

For a comprehensive view of the recent additions to our knowledge on this subject we are indebted to the work of Donald Hunter, and in this brief résumé of the present position I freely acknowledge that indebtedness.

In the first place, I should like to say a few words on the association between the thyroid gland and calcium metabolism.

In hyperthyroidism the output of calcium may be increased two to eightfold, and out of all proportion to the increase in the basal metabolic rate. In this condition, much of the calcium is excreted by the bowel, and that without any excess of calcium in the blood. This increased output cannot be due to the thyroid stimulating the parathyroid, or the blood-calcium would be high. Yet like the parathyroid, the thyroid appears to mobilize the calcium from the bones—in less than half the cases, osteoporosis occurs—but it can be prevented by an adequate calcium diet. It is produced by progressive bone absorption by osteoclasts.

But it is naturally in connection with the parathyroids that the question of calcium metabolism has recently come to excite special interest. I want to contrast the effects of parathormone and vitamin D on calcium metabolism and then to apply this to certain clinical conditions.

Although the rôle of the red bone-marrow in the formation of red corpuscles has been known for over sixty years, and for more than half that time it has been recognized that the amount and distribution of blood-forming marrow was not fixed, but fluctuated according to the needs of the organism, it is only recently that we have known that the same applies to the calcified structures of the bone as well. In the skeleton we have a great calcium bank where deposits are continually being paid and withdrawals made.

Although from the earlier days of the experimental study of total removal of the thyroid, tetany was connected in many people's minds with the coincident removal of
the parathyroids, it was not until 1909 that MacCallum and Voegtlin showed that the connecting link was the fall in blood-calcium. However this is produced, whether by parathyrectomy or otherwise, tetany will follow. The preparation by Collip of an active hormone from the parathyroids known as parathormone, led to the recognition of the opposite condition of hypercalcæmia. How little the mechanism of this was understood at first, is shown by the fact that the parathyroid hormone was given to assist the union of fractures, and in 1925 Mandl actually transplanted parathyroid tissue into a patient suffering from the condition of extensive decalcification of bone known as osteitis fibrosa. In the same year, however, Hoffheinz showed that parathyroid overgrowth was present in this condition, and it was recognized that parathormone produced a rise of calcium in the blood by abstracting it from the bones and muscles, particularly the bones.

So much for the broad facts about parathormone; now as to vitamin D. I need not recall the history, however interesting it may be, of the controversy between those who attributed rickets to faulty diet, and those who considered it a disease of the dark. As so often happens when sincere and skillful workers differ, both were right. The discovery that light could act on ergosterol to give rise to vitamin D which can now be prepared in practically a pure state as calciferol is a romance of post-war medicine, the initial steps were taken by British scientists in the relief of starving Vienna. In future this discovery may come to be regarded as one of the very few useful outcomes of the War.

Now, just as we have hypoparathyroidism represented by low blood-calcium, tetany, opacities in the lens and damage to ectodermal tissues generally, as against hyperparathyroidism represented by high blood-calcium and decalcification of bone, so we have avitaminosis and hypervitaminosis. Where vitamin D is concerned its lack causes rickets and its excess produces symptoms which in several respects recall hyperparathyroidism. But there are several important differences, and it is by a study of these differences that we may hope to obtain a clearer conception of calcium metabolism in general.

In vitamin D deficiency, the salient point is that the net absorption of calcium is decreased. By net absorption we mean the gross absorption less the amount re-excreted into the bowel. The calcium changes associated with the parathyroid, on the other hand, occur in animals deprived of their intestines. In clinical rickets the blood-phosphorus and calcium may both be low. Inadequate calcification results, but it is primarily a disease of the blood rather than of the bone.

The preparation of a concentrated vitamin D, such as irradiated ergosterol, was followed by the recognition of its toxic action when given in excess. It then produces increased net absorption, a tendency to high blood-calcium and phosphorus, excessive formation of densely calcified new bone, and a deposit of calcium in soft tissues particularly the kidney and the aorta. It is interesting to note that these two structures are specially rich in phosphatase, the enzyme which is concerned in depositing calcium. The serum of rats in which hypervitaminosis has been induced will even cause heavy calcification in slices of bone in vitro. The toxic effects are not due, as was at one time thought, merely to the alcoholic solution of vitamin D, for they can be produced by pure calciferol (L. F. Harris, Lancet, 1932, vol. i, p. 1031).

Now it is a striking fact that when maximal toxic overdoses of vitamin D are given,
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a reabsorption of bone occurs if there is no increased provision of calcium in the diet. It looks as if the bone is called upon to provide calcium when the available supply from the gut falls short. And it will fall short since the animal begins to refuse food. In hyperparathyroidism and severe hypervitaminosis, we have then these striking features in common—high blood-calcium, deposits of calcium in the kidneys, and reabsorption of bone. It is not surprising, therefore, that the actions of parathormone and vitamin D have been held to be correlated—that vitamin D stimulated the parathyroids, and that in the absence of these glands vitamin D could no longer raise the blood-calcium. That has been disproved and this difference stands out. Vitamin D increases the net absorption of calcium and phosphorus, parathormone merely raises the blood-calcium by withdrawing calcium from the bones and actually leads to a loss of calcium in the body through the kidney. Now that these facts are clearly recognized, surely it behoves us to reconsider the clinical use of parathormone. As Leslie Harris says (Lancet, 1932, vol. i, p. 1035), “It may be conceded that as an emergency measure in tetany the use of parathormone is admissible, to bring about a rapid cure of hypocalcaemia; but its continued use, we wish to suggest, is to be deprecated, since it tends merely to aggravate the underlying error by diminishing still further the inadequate retention of calcium and withdrawing still more mineral from the impoverished bone. That parathormone has proved invaluable after parathyroidectomy, of course needs no emphasizing, but unfortunately there appears to be a tendency in some quarters to prescribe it, rather than vitamin D, whenever a calcium deficiency is suspected, and, in fact, certain parathyroid preparations are still advocated for rickets, nutritional tetany, and ‘disorders of calcium metabolism’ generally.”

Now, I think we have here the explanation of something which has puzzled me a good deal in the past. It had been noted that repeated injections of parathormone lost their beneficial effects. The first case of post-operative tetany treated by Collip's hormone in 1925 died in 1929, in spite of 160 units daily reinforced by massive doses of calcium lactate; even then the blood-calcium was only 6'9 mg. per cent., and transplantation of two parathyroids had no evident result. It would be disturbing to our whole conception of hormones if they acted as antigens, but at first it looked as if parathormone did excite the production of its own antidote. Now we see that keeping up the blood-calcium at the expense of the bones is a measure which must defeat itself in time. It is clear that in such cases we should rely on vitamin D rather than on parathormone, just as we do in the treatment of rickets. At the same time, it is important to realize that there are risks of producing hypervitaminosis clinically. The optimum therapeutic dose is not so far removed from the toxic as to enable us to play carelessly with concentrated preparations of vitamin D. There is a consensus of opinion that 1 mg. of irradiated ergosterol daily is adequate for an average case of rickets. Cases of renal calculi have been recorded after continued administration of 4 mg. daily; and this has led to a fatal issue in two reported instances. (Putscher, Thatcher, quoted by Harris.) It is almost impossible to produce hypervitaminosis by natural food-stuffs, but W. E. Dixon suggested that excessive production of irradiated ergosterol by exposure of the skin to the sunlight may play a definite part in increasing the frequency of renal calculi in the tropics.

It is extraordinary what a small group of wave lengths in the ultra-violet are capable of converting ergosterol into calciferol, and how effectual a sheet of glass is in excluding
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them; even vita-glass requires only a thin film of dust on it to do the same. As to the clinical use of ultra-violet rays, Miss Chick has stated that they are only useful when it is desired to raise the calcium in the blood, and that there is no scientific evidence worth the name that they do good at all in any other condition.

Having thus somewhat dogmatically cleared the ground, I will proceed briefly to discuss certain bone diseases in the light of these observations.

In generalized osteitis fibrosis the calcium is raised and the phosphorus is lowered in the blood. Satisfactory proof of hyperparathyroidism now exists in thirty-two such cases. Renal calculi are common. The removal of the parathyroid tumour usually abolishes the bony pains at once, sometimes the renal calculi begin to break up. The normal conditions of calcium and phosphorus in the blood and urine return to normal. It is interesting that tetany is common after operation even before the blood-calcium has fallen to normal. One may conclude that the body becomes habituated to a higher level, just as in the earlier days of insulin treatment, we found that chronic diabetics could not stand too rapid a reduction of their blood-sugar, for they showed hypoglycemic symptoms with a blood-sugar still above the normal. In view of the extensive destruction of the architecture of the bone, we must not expect too much from operation, though the osteoclastic tumours have been observed to disappear.

At first sight osteitis deformsans (Paget's disease) appears to be the diametrical opposite to osteitis fibrosa. Yet in both there are two similar processes going on; apposition of new periosteal bone, and reabsorption of cancellous bone. In osteitis deformsans the apposition, and in osteitis fibrosa the reabsorption predominates. In osteitis deformsans the calcifying enzyme, phosphatase, is always present in excess, but the parathyroids are not involved, and the blood-calcium and phosphorus are approximately normal. Recently some extraordinary successes with ultra-violet rays have been recorded in the treatment of osteitis deformsans. In the light of what has already been said, this would suggest that a failure of net calcium absorption and an excess of calcifying enzyme are the principal factors in the disease, and that the histological resemblances between it and osteitis fibrosa are only another example of the simulation of parallel changes due to disturbances of parathormone and vitamin D metabolism which on deeper analysis will prove to be illusory.

In osteogenesis imperfecta, instead of excess of osteoclasts, there is failure to produce osteoblasts. The children look infantile and stunted, and fractures from slight trauma are common. Three other defects are commonly associated with it—blue sclerotics, a tendency to dislocation of the joints, and after the age of 20 otosclerosis. No constant changes in calcium or phosphorus have been demonstrated. Garrod classes it as one of the inborn errors and familial transmission is well established.

In rickets the importance of vitamin D is now completely proved but it should be noted that as long as the proper calcium-phosphorus ratio in the food is observed, rickets does not develop, even in the complete absence of antirachitic substances from the diet. But if the ratio is markedly disturbed either way, rickets develops as soon as vitamin D is deficient. Experimentally there is a low phosphorus rickets, histologically resembling the clinical form, and a low calcium rickets, which shows osteoporosis as well.

Osteomalacia and hunger osteopathy are really similar in ætiology to low calcium rickets and yield to similar treatment by vitamin D. As might be expected with this
low blood-calcium, tetany is not uncommon. The association between the two conditions is further shown by J. P. Maxwell’s X-ray evidence of antenatal rickets in osteomalacic mothers in China.

**Coeliac rickets** and spontaneous fractures occasionally occur in the form of infantilism accompanied by severe intestinal indigestion described by Gee as the “coeliac disease” which is not believed to be due to defective fat absorption. The blood-calcium is low and tetany common. It can be completely cured by ultra-violet rays or irradiated ergosterol. In the statorrheas of adults, including sprue, bony deformities, low blood-calcium and tetany frequently occur. Achlorhydria is common, but the chief factor is the failure to absorb vitamin D as this is so closely bound up with the absorption of fats.

**Renal rickets** presents a very interesting problem. Renal dwarfism or infantilism due to nephritis in early life was first pointed out by Morley Fletcher in 1911, and reinforced by Hugh Barber in 1913. The bony changes come on later, usually just before puberty. They are not due to true rickets or to any lack of vitamin D. The chronic nephritis is responsible for disturbing the calcium and phosphorus metabolism. Howland in 1916 showed that the nephritic kidney excretes phosphorus with difficulty, while Izod Bennett and others have emphasized the drainage of calcium into the urine in this condition. Thus, the phosphorus rises and the calcium falls (the exact opposite of osteitis fibrosa) so tetany is common in addition to the bony changes of which genu valgum is generally the earliest to appear.

The following table shows the changes in the blood, bone and kidneys, and in catalytic agents such as parathormone, vitamin D and phosphatase in these various conditions. The association of tetany with a low blood-calcium is clearly seen.

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<tr>
<th>Blood</th>
<th>Catalyte</th>
<th>Tetany</th>
<th>Principal bony changes</th>
<th>Kidneys</th>
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<td>Osteitis fibrosa</td>
<td>Hypervitaminosis D</td>
<td>Rickets</td>
<td>Osteomalacia</td>
<td>Renal rickets</td>
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**Reviews.**

**Orthopaedic Surgery.** By Walter Mercer. Arnold and Sons.

After reading this book one must repeat the remarks of Professor Fraser, that Mr. Mercer has contributed a most readable and practical treatise on the subject of Orthopaedics.

Even as yet many practitioners regard orthopaedic surgery in the light of an absolute well-defined surgical specialty, and may be rightly so too, but in this volume the author has dealt with it from the view-point of the general surgeon, and this fact will be greatly appreciated.

It is a very lucid exposition of the Principles and Practice of Orthopaedics as taught in the Edinburgh school, and without sacrificing material for brevity, he has produced a comprehensive yet concise survey of the subject.
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