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THE CLINICAL BEARINGS OF THE PARATHYROIDS

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In this paper I propose to deal with the general principles underlying the action of the parathyroid glands, illustrating their clinical importance by such items as have fallen within my experience. Those who desire more detailed information are referred to one of the many reviews published on this subject, of which the most recent, by Hunter (1937), might be specially mentioned.

The parathyroids are small glands, usually four in number, situated at the postero-lateral margins of the thyroid. Occasionally one or more additional glands may be found, either similarly situated, or placed above or below the thyroid—even, in a few instances, within the superior mediastinum. The maximum total weight is less than 0.5 gramme. Histologically they consist of closely packed cells of two main types—"principal cells" with a faintly basophil protoplasm, and eosinophil cells. We have no evidence to indicate definitely the relative importance of these types.

The Parathyroid Hormone

The glands produce a hormone which has been extracted by Collip in a form suitable for intravenous injection, but which has not yet been prepared pure enough for its chemical constitution to be determined, and hence no synthetic preparation of it has been possible. For clinical purposes several commercial extracts of recognized activity are available, though doubts are sometimes expressed regarding the uniformity of their potency. At present a unit is defined as one-hundredth part of the amount necessary to raise the blood calcium of a dog weighing 20 kg. by 1 mg. per 100 c.cm. The hormone is useless when taken by mouth.

Although it is generally agreed that the parathyroids are primarily concerned with regulation of calcium and phosphorus metabolism, and that the various other manifestations of increased or decreased activity are only secondary to this function, the precise mechanism by which the hormone acts has not yet been fully worked out. Several theories have been put forward suggesting that the primary influence is exerted on one or other of the calcium fractions and even on phosphorus metabolism.

From the point of view of the clinician it will suffice to state clearly what appears to be the most likely sequence of events. The activity of the parathyroid is normally governed by the level of serum calcium, probably the ionized fraction. A fall in value of ionized calcium acts as a stimulus to secretion which may operate either directly or indirectly; if indirectly, then either through a nervous mechanism or by stimulating the pro-

duction of a parathyrotropic hormone by the pituitary. The primary object of this increased secretion is to restore the level of serum calcium to its normal value, as this is essential for proper functioning of the greater part of the neuro-muscular system. The object is attained by the stimulation of osteoclastic activity in bone, so that the balance normally maintained between deposition and absorption of calcium is upset and calcium salts are released to the blood in increased quantities.

It is not necessary to ascribe any further direct action to the parathyroid hormone, for the results of interference with the supply of hormone available either in clinical or in experimental conditions will follow from this primary effect. Suppose the supply of hormone is deficient. Osteoclastic activity is retarded, and since osteoblastic activity proceeds unchanged there is a lowering of serum calcium, resulting in clinical tetany and reduced calcium excretion. It is generally found that the concentration of inorganic phosphorus in plasma varies inversely as that of calcium, possibly as an expression of the law of mass action. Hence a further feature will be a high plasma inorganic phosphate content. The only other result which might logically be expected would be an increase in calcium content of bone. Tetany is an acute condition which must be treated at once, so that it would be impossible to demonstrate such increase of calcium content. It would be very interesting to know if any patient with chronic parathyroid deficiency who had lived for any considerable time while receiving calcium injections showed any observable increase in density of x-ray shadows.

Events parallel to those in the above sequence follow a prolonged increase in available parathyroid hormone. There is a stimulation of osteoclastic activity, so that absorption of calcium from bones outruns deposition, resulting in an increase in serum calcium. This in turn causes a reduction in muscle tone, an increased calcium excretion, and lowered plasma inorganic phosphate. The condition can continue either experimentally or clinically long enough to produce a definite reduction in bony calcium as shown by x-ray shadows, by loss of strength, and by appearance on direct examination.

Hypoparathyroidism

In man, clinical hypoparathyroidism and hyperparathyroidism present further features which call for special consideration. Hypoparathyroidism may result either from removal of parathyroid tissue during an operation on the thyroid or from a spontaneous loss of function,

and in both cases the primary fall of serum calcium gives rise to those secondary changes referred to above. Outstanding among these is the increased neuro-muscular excitability or tetany. In the post-operative type symptoms begin twenty-four to seventy-two hours after operation, and generally vary in severity with the reduction of serum calcium. The severity seems to be more closely related to the difference between pre-operative and post-operative values of serum calcium and the rate at which serum calcium falls than to the absolute value at the time tetany sets in. Thus in a person whose blood calcium was constantly in the neighbourhood of 14 mg. per 100 c.cm. before operation, removal of a nodule of hypertrophied parathyroid tissue caused an immediate fall of serum calcium to 8.5 mg., which resulted in tetany, although people whose serum calcium had been normal do not develop tetany until a value of about 7 mg. per 100 c.cm. has been reached. The condition may at first be latent—that is, neuro-muscular excitability is demonstrated only by the application of specific stimuli, as in Trousseau's and Chvostek's signs. Later the skeletal muscles develop spasms, apparently spontaneously. The characteristic attitudes produced in the forearms and hands, and often in the legs and feet, have given rise to the term carpo-pedal spasm. Disorders of sensory nerves producing tingling sensations in upper and lower limbs are present early in a number of cases. Patients who have suffered from hypoparathyroidism for some time are said to develop subjective manifestations: they tend to become hysterical and to be unduly depressed even between acute attacks. In rare cases cataracts may appear.

POST-OPERATIVE TETANY

Post-operative tetany is often due to temporary interference with the blood supply of the glands, and will rectify itself when an adequate supply is re-established. Only in those instances where a considerable amount, say 50 per cent., of the total parathyroid tissue is removed will tetany persist. In both cases the logical treatment is injection of parathyroid extract to make good the deficiency in the natural supply and the administration of calcium to correct as quickly as possible the lowering of serum calcium.

The essential factor in the production of tetany is a low serum calcium, and any condition which produces this will lead to increased neuro-muscular excitability like that found in parathyroid deficiency. Thus any interference with calcium absorption, such as is produced by an excess of fatty acid in the intestine or by a deficiency of vitamin D, will operate in this way. An interesting point which has been made in connexion with the tetany associated with vitamin D deficiency is the lack of parallelism between the severity of the rickets and that of the tetany. In a series of cases of tetany published by Guild (1933) 58 per cent. had very mild rickets, while only 6 per cent. showed really severe bony changes radiologically. No attempt was made in the original paper to account for this peculiarity, but in view of what has been said above a rational explanation could be given as follows. In one type of case suffering from lowered calcium absorption the tendency to the lowering of blood calcium stimulates the parathyroids, and calcium is mobilized from bones. Tetany is thus prevented, but the bones suffer correspondingly. In another type with less active parathyroids calcium is not mobilized from bones, and the blood calcium falls. Tetany develops, but the bones will not be so severely damaged. Since the principal function of the parathyroids is probably to maintain the level of blood

calcium, tetany produced by a low calcium absorption is to be regarded as a sign of relative failure of parathyroid activity under strain. Tetany due to lowered calcium absorption should be treated by improving the factors promoting absorption. Injections of calcium salts and parathyroid extract may be employed, but the latter should be regarded as only an emergency measure.

One other condition may be touched upon before leaving the subject of hypoparathyroidism. A number of authors, of whom Mirvish (1930) may be specially mentioned, claim to have shown that the local pathological condition in otosclerosis is a manifestation of parathyroid deficiency and that the disease may be successfully treated by injection of extract. But the figures given for serum calcium by this author are normal, and other workers have failed to produce permanent benefit consistently by this treatment.

Hyperparathyroidism

Hyperparathyroidism may be brought about by injection of the extract of the parathyroids or by the local manufacture of an excess of the hormone by parathyroid tissue. In animals the prolonged injection of the extract produces the effects summarized above. In man it is not possible or desirable to continue the experiment long enough to produce obvious bony changes, but a good deal of information has been obtained from cases of lead poisoning treated by parathyroid extract. Here lead is deposited in the skeleton, and this acts as a reservoir long after the supply from outside has been cut off. Injection of parathyroid extract causes a rise in serum calcium, with increased calcium excretion. At the same time evidence of its action on the bones is produced by the increase in excretion of lead and its disappearance from these reservoirs.

Clinical hyperparathyroidism due to an increased local production of the hormone by a tumour has recently assumed special interest in view of the discovery that it is responsible for generalized osteitis fibrosa cystica. Although this was described in 1891 by von Recklinghausen, and post-mortem examination during the early part of this century had repeatedly shown cases to be associated with a parathyroid tumour, it was not until 1926 that Mandl attempted to cure the disease by removal of such a tumour. The case showed the typical features to be described presently, and the operation effected a complete cure. This discovery, taken in conjunction with the observed effects of the injection of Collip's extract, finally established the role of the parathyroids in calcium metabolism, which, in spite of significant observations by MacCallum and others, had not previously been definitely recognized.

The Development of Clinical Hyperparathyroidism

We may trace the development of the clinical condition as follows. The primary effect is stimulation of osteoclastic activity with removal of calcium salts from bones. Secondary effects are produced in the bones and elsewhere. In the bones we find loss of rigidity, leading to deformity, spontaneous fractures, pain, and tenderness. Radiologically and histologically there are lack of density of x-ray shadows, cyst formation, giant-celled tumours, replacement of bone by fibrous tissue, and increased osteoblastic and osteoclastic activity with osteoporosis. The general alteration may be quite easily seen with the naked eye, and the bone may be so soft as to be easily cut with a knife.

The more general effects may be largely attributed to the increase in blood calcium which automatically follows removal of this element from the skeleton. Thus plasma inorganic phosphate is lowered, muscle tone is diminished, and calcium excretion is increased. The last leads to polyuria, which in turn produces polydipsia. The continual passage of urine rich in calcium salts, often together with the bedridden condition of the patient, leads to deposition of calcium salts in the kidney, either diffusely in the cortex or as one or more renal calculi. Deposits of calcium phosphate may also be found in the lungs.

A further interesting feature of this condition is the great increase of plasma phosphatase. This enzyme is concerned in the hydrolysis of esters of phosphoric acid, with the liberation of inorganic phosphate. It normally occurs in greatest quantity in osteogenetic tissues, and is found in blood only in very small concentrations. In hyperparathyroidism it is present in plasma in five to ten times the normal values, and we assume that this is due to a marked compensatory activity of osteoblastic tissue. Certain American workers—for example, Ballin (1932)—have described a reduction of the R-T interval in the electrocardiogram. This they suppose to be a direct effect of the raised blood calcium on the relaxation of the heart.

The sequence of events may be represented diagrammatically as follows:

The victim of the fully developed condition is thus not infrequently a confirmed invalid who has been much restricted in activity or completely bedridden, perhaps for years. In the absence of treatment, death, often from renal complications, was the rule. The dramatic improvement after removal of the tumour is therefore all the more striking. The blood calcium falls, often so rapidly that symptoms of tetany supervene and require treatment by injections of calcium salts or parathyroid extract; blood phosphate and calcium excretion return to normal, while bone pain and tenderness and muscular atony disappear, and the patient regains strength and weight rapidly. The bones return to normal more slowly, but

definite increase in density is generally apparent in six to twelve months. The cysts may decrease in size, and there are no more spontaneous fractures. In short, the patient has always been improved, and has in many cases been enabled to lead an active, useful life.

When the condition was first recognized it was thought that hyperparathyroidism might prove to be a not uncommon complaint, as many clinicians realized almost immediately that they had cases already under their care; but general experience indicates that it is quite rare. In Dublin only six cases, proved by operation or necropsy and full investigation, have been seen during the last seven years. Three of these have already been described in detail by me (1936).

It has also been stated that a parathyroid tumour is a frequent cause of renal calculi. Colby (1934) has recorded three cases, in two of which no bone change was detected radiologically but which showed a raised serum calcium. A parathyroid tumour was found in each case and was removed, and in one the calculus disappeared after operation. But in the urological department of the Meath Hospital, Dublin, during the last five years every patient with urinary calculi has been investigated from this point of view, and not one case has been found.

Several attempts have been made to include other bone diseases, such as osteitis deformans, osteogenesis imperfecta, and polyarthritides, as manifestations of hyperparathyroidism, but the evidence adduced is in no case conclusive. Certainly, in several cases of osteitis deformans and in one case of osteogenesis imperfecta we found no biochemical evidence of increased parathyroid activity, and in the last-mentioned a post-mortem examination failed to reveal a parathyroid tumour.

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The Proceedings of the Second International Scientific Congress on Nutrition have been published under the title *La Science de l'Alimentation en 1937* (Alençon, Imprimerie Alençonnaise). Among the numerous resolutions adopted by the congress were the following: that tables of analysis of foods in terms of minerals, vitamins, and indispensable organic compounds should be drawn up and periodically reviewed in every country; that it was desirable to popularize the rules of a rational diet based on modern scientific knowledge and to establish closer relations between (a) physiologists and doctors, (b) public authorities, and (c) families and educational establishments; that children should not have more than 1 litre of milk a day; that in homes for infants, in schools, etc., bread, pastries, dried vegetables, pork, and recooked meats should to a large extent be replaced by fresh vegetables and fruits; that from the age of 8 years it was necessary to give an abundant ration of animal protein; that a child of 12 needed a diet as nutritive and as varied as that of an adult, and that a boy or girl of 16 required a greater amount of food than the average adult of either sex. Various resolutions were also passed which emphasized the importance of continuing investigations in different countries into the diet of people of different professions and occupations, the importance of education in dietetics, the need for legislation for preventing the infection of food, the importance of refrigeration, and the control of advertisements which exaggerated the good effects of vitamins.