ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

THE PARATHYROID GLANDS

BY

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The parathyroid glands are the smallest known endocrine organs in the body. Usually there are four glands, a superior and an inferior on each side, but in about 7 per cent. of subjects five or six are found, the additional glands being distributed equally between the upper and lower positions. The superior glands are found on the middle third of the posterior border of each lateral lobe of the thyroid, and the inferior glands are placed very close behind the lower pole. About 10 per cent. of parathyroid glands are within the thyroid capsule, but it is very rare indeed to find them buried within the substance of the gland. In 22 per cent. of subjects one or more parathyroids occur in the upper pole of the main thoracic thymus or its involuted remains, but in about only 1 per cent. of subjects is the gland actually within the thorax. A normal parathyroid has been found as low as 11 cm. beneath the lower pole of the thyroid, embedded in the thymus opposite the auriculo-ventricular groove. A normal parathyroid has been observed above the level of the upper pole of the thyroid, in the carotid sheath, 2 cm. below the bifurcation of the common carotid artery.

The colour of the parathyroid glands is pinkish- or brownish-yellow, contrasting sharply with the deep red brown of the thyroid. The normal glands are always difficult to distinguish at operation. After partial thyroidectomy identification of parathyroid tissue in the thyroid removed is very difficult, and an experienced surgeon may prove to be correct only in 5 per cent. of cases when checked by histological methods.

In adults over 20 the average weight of the four parathyroid glands together is 132 mg., but weights varying from 66 to 388 mg. have been recorded. The average size in persons over 20 years of age is 6.5 by 3.5 by 1.5 mm., the lower glands being slightly larger than the upper, and the female glands rather larger than the male. No normal gland ever exceeds 4 mm. in thickness, but occasionally a length as great as 15 or even 20 mm. is encountered. Corresponding to this elongation the other dimensions of such glands are usually small—that is, they are long, narrow, and thin (Gilmour and Martin, 1937).

Histologically two types of cell are readily distinguished: the oxyphil and the principal. There are sub-varieties according to the depth of staining. The two types do not appear to be of distinct origin or nature, but rather to represent conditions of special activity. It is not known which cell gives rise to the active substance on extraction of the gland.

The Hormone

The clinical use of the active principle of the parathyroid glands is dependent upon its marked influence on calcium and phosphorus metabolism. Its physiological effects are to raise the blood calcium and lower the blood phosphorus, possibly to increase the ionized calcium in the blood, and to increase the calcium and phosphorus excretion in the urine. The calcium for this increased

demand comes either from the stores of calcium salts in the bones or from a large amount of ingested calcium salts (Aub, 1929). Parathyroid extract is obtained from the fresh parathyroid glands of healthy domesticated animals used for food by man. The glands are freed from gross fat and connective tissue, ground, and extracted with hydrochloric acid. The aqueous extract of the active principle is purified to make it suitable for parenteral administration, and is sterilized by heating. The preparation is usually sold in 5 c.cm. vials capped with rubber diaphragms, and containing 100 units in each c.cm. The *British Pharmacopoeia* includes no preparation of the hormone.

There is no standard for parathyroid extract, and the unit is based on the rise in blood calcium produced by injecting the extract either into normal dogs or into dogs from which the parathyroid glands have been removed. The unit first adopted was defined as one-hundredth part of the amount necessary to raise the blood calcium of a dog weighing 20 kilogrammes by 5 mg. per 100 c.cm. The *U.S.P.* XI (1936) reduced the strength of the unit to one-fifth of its previous potency. The doses referred to in this paper are expressed in *U.S.P.* units. Confusion as to the potency of parathyroid preparations is bound to remain until a standard preparation becomes available. Standardization is being attempted (1) by estimating the rise in the urinary calcium of groups of rats, and (2) by employing the awakening effects of parathyroid extract on the narcosis produced in mice by injections of magnesium sulphate (Dyer, 1936). These methods involve a comparison of the potency of preparations of unknown strength with those of a standard preparation. The results give promise of a suitable method of preparing a stable powder which may serve as a standard until the pure hormone has been isolated. The following preparations are to be obtained: parathyroid extract—Lilly, N.N.R. (parathormone); parathyroid extract—Squibb, N.N.R.; paroidin, N.N.R., Parke, Davis and Co.; and euparitone, Allen and Hanburys.

Parathyroid extract is destroyed in the alimentary tract and is therefore worthless when given by mouth. Some commercial houses manufacture parathyroid tablets, but of such firms it may be truly said that their enterprise outruns the discretion of their scientific advisers.

DOSAGE

Like other hormones, parathyroid extract has a greater effect when it is needed; thus, 75 units a day may be enough to raise the serum calcium from 4.5 to 7 mg. per 100 c.cm. in a case of low-calcium tetany. In normal individuals it may require 500 units a day to raise the level from 10 to 12 mg. per 100 c.cm. Susceptibility, however, varies greatly, and a dose which will elevate the serum calcium considerably in one individual may have little effect in another. The dosage must be regulated by estimations of the serum calcium, repeated every few days until the new level becomes constant. If the doses given are too small, this can, of course, be detected by persistence of the tetany. A serum calcium level above 12 or 13 mg. per 100 c.cm. is never desirable. Since hypercalcaemia gives few clinical indications until a level of about 14 mg. per 100 c.cm. is reached, the need for repeated estimations will be appreciated. Where hypercalcaemia persists, loss

of appetite, nausea, and a sense of fatigue appear. Repeated doses of parathyroid extract are more often effective than a single large injection. It is therefore wiser to give the extract twice daily, even though the injections may cause some induration and pain.

PARATHYROID OVERDOSAGE

When given in excess parathyroid extract causes the inorganic phosphorus in the blood to rise as well as the calcium. The efficiency of the kidneys is interfered with and nitrogenous waste products accumulate in the tissues. Owing to the large excretion of calcium and phosphorus in the urine renal calculi may be formed, and metastatic calcification may occur in the kidneys, stomach, and lungs. The activity of osteoclasts is increased, and this leads to excessive resorption of bone with osteoporosis and osteoclastic (giant-celled) tumours. The activity of osteoblasts is also increased, but the apposition of new bone cannot keep up with the destruction of old (Thomson and Collip, 1932).

TIME RELATION

The parathyroid hormone injected intravenously has a latent period of approximately four hours, after which the blood calcium rises and therapeutic effects begin. These effects last about twenty hours following a single injection. In emergency it must be remembered that calcium salts when injected intravenously exert an immediate effect, which is often prolonged for two hours or more. The chief disadvantage of the parathyroid extract now available is the gradual loss of its effect. After injections have been repeated for several months an apparent immunity is established, and then 750 units may have no result in a patient who originally responded well to 50 units. This characteristic limits the use of parathyroid extract to acute conditions, in which the treatment is to be continued for weeks rather than for months.

THE PARATHYROTROPIC PRINCIPLE OF THE PITUITARY

It has been reported recently that the urine of patients with hyperplasia of the parathyroids contains a substance which will induce hyperplasia in the parathyroids of normal rabbits. It has also been claimed that parathyroid enlargement may be produced in the rat by the administration of a pituitary extract: this is attributed to a parathyrotropic hormone. Similarly, an increase in blood calcium in rabbits has been reported after the administration of a parathyrotropic pituitary extract: the additional claim is made that this is due to the stimulation of the parathyroids, since the extract has no effect after parathyroidectomy. It therefore seems possible that the activity of the parathyroid bodies is directly controlled by the pituitary.

Hypoparathyroidism

Parathyroid insufficiency occurs in clinical medicine both as post-operative tetany following operations upon the thyroid or the parathyroids and as spontaneous hypoparathyroidism, which is analogous to myxoedema. Both conditions are rare. Parathyroid insufficiency results in lowering of the serum calcium with an associated rise in the plasma inorganic phosphorus, diminished urinary excretion of calcium and phosphorus, and the clinical picture of tetany.

TETANY

As its name implies, tetany is a condition characterized by a tendency of muscles to go into a condition of painful, prolonged spasm. This commonly involves the muscles of the forearms and hands, the larynx, less fre-

quently the muscles of the legs and feet, and even the oculomotor muscles. Sympathetic motor fibres may be involved, resulting in spasm of the cardia, pylorus, or any smooth muscle. Sensory nerves are also affected, and paraesthesia of the forearm and hand, often of ulnar distribution, is the most constant symptom of tetany. A similar tingling sensation may be felt in the legs, especially in the distribution of the sciatic nerve. In the crises of tetany the patient may complain of girdle sensations, of a feeling of a great weight on the chest, and of general numbness. The central nervous system may be affected: drowsiness is common, and twitchings, followed even by convulsions and coma, may occur. Even when there are no major manifestations of tetany between attacks the patient may be nervous, self-centred, introspective, difficult to handle, hysterical, emotional, or depressed.

The underlying condition appears to be a decrease in available calcium ions, usually associated with a serum calcium level below 7 mg. per 100 c.cm. The plasma phosphorus figure rises to 5 mg. per 100 c.cm. or higher. There is a diminished excretion of calcium and phosphorus in the urine. Though in severe crises the serum calcium usually is between 4 and 6 mg. per 100 c.cm., the severity of the symptoms does not vary in proportion to the level of the serum calcium figure. Probably it varies inversely with the number of calcium ions in the body fluids, but at present there is no means of measuring this. The symptoms generally become mild or disappear when the serum calcium rises above 8 mg. per 100 c.cm.

The recognition of tetany is easy during an attack. There is flexion of the metacarpo-phalangeal joints with extension of the interphalangeal joints, the thumb and little finger being drawn into the palm. There may be flexion at the wrists and elbows and slight pronation of the forearm. The carpal spasm is characteristic, and its association with tingling of the arms and sometimes of the legs, with or without hoarseness or stridor, completes the picture. The hysterical patient who knows a little about tetany is as a rule unaware of the constancy of the paraesthesia and can seldom reproduce true carpal spasm. The diagnosis can be confirmed by two clinical tests.

1. *The Chvostek Sign.*—This consists of twitching of the upper lip or even of one-half of the face, and is elicited by tapping the facial nerve just in front of and below the ear. It is not an absolute sign of tetany, for it may be demonstrated occasionally in healthy people.

2. *The Trousseau Sign.*—This consists of typical carpal spasm brought on by pressure on the upper arm. It is best demonstrated by placing a sphygmomanometer bag on the arm and inflating it to a figure just above the systolic blood pressure. Within a few seconds or up to one minute spasm appears and gradually increases. The spasm becomes very intense in patients with tetany, so that the thumb can be separated from the palm only with difficulty. In simulated tetany it is relatively easy to pull the thumb away from the palm and to demonstrate voluntary contraction on the part of the patient.

CATARACT

Lesions of ectodermal tissues may arise in patients suffering from long-standing tetany. Cataract, brittleness and ridging of the nails, loss of hair, and defects in the enamel of teeth giving rise to several transverse ridges one above the other—all these defects in ectodermal tissues have been described in tetany. None of these changes is common, but the first is met four times as frequently as

any of the other three. The association of cataract with tetany was first recorded about fifty years ago. It has been described in endemic tetany, post-operative tetany, rickets, and spontaneous hypoparathyroidism. It may appear even in young people and may require operative treatment. It is now possible by means of the slit-lamp to detect opacities in the lens in cases in which no visual disturbance exists, neither does it follow that such a patient will necessarily develop such disturbance later.

POST-OPERATIVE TETANY

In countries where operations for endemic goitre are common post-operative tetany is more frequently met with than here; but now that radical thyroidectomy is becoming a common practice, especially in exophthalmic goitre, it is probable that more cases of tetany will be seen. Where post-operative tetany supervenes after a subtotal thyroidectomy it usually does so in from one to four days. It is an uncommon complication, and is generally found in patients who have had a previous operation upon the thyroid gland. The patient begins to feel tinglings in the arms and hands on the second or third day. This tends to become more intense and more widespread on the fourth day, when attacks of carpal spasm, perhaps associated with hoarseness or stridor, appear. Between attacks, which may last from a few moments to an hour or more, the patient suffers from persistent paraesthesia, most marked in the arms, often from stiffness of the hands or mild carpal spasm, and perhaps from hoarseness. In most cases, after the initial rather sudden onset, the symptoms moderate and gradually disappear, never to return. Here there is probably pressure due to the trauma at the site of operation, which, together with oedema and blood clot, causes temporary interference with the blood supply of the glands. There are, however, severe cases which go on to chronic tetany, and here it is probable that the greater part of the parathyroid tissue has been removed at operation. In the state of chronic tetany paraesthesia is by far the most constant symptom. It becomes worse when the patient is worried or tired. There may be nervousness, lack of energy, weakness, and fatigue. Superimposed upon this chronic state of ill-health are crises of carpal spasm. Some patients are almost incapacitated by prolonged spasms with severe paraesthesia and hoarseness. In others the symptoms are very mild and the spasms infrequent. In all cases the condition is liable to be aggravated by acute infection, malnutrition, unhappiness, or fatigue.

Tetany often arises after removal of a parathyroid tumour in hyperparathyroidism. In some 7 per cent. of cases it has proved fatal.

SPONTANEOUS HYPOPARATHYROIDISM

Spontaneous or idiopathic hypoparathyroidism is a very rare disease. It affects persons of either sex and at any age. The onset is gradual, the first symptoms being ulnar paraesthesia, weakness, and loss of energy. Later, attacks of tetany supervene and the course of the illness is similar to that of post-operative tetany. The serum calcium may be as low as 5 mg. per 100 c.cm., and the plasma phosphorus as high as 10 mg. Lenticular opacities may occur and advance to cause blindness (Albright and Ellsworth, 1929).

Differential Diagnosis

Tetany may result from a number of causes, including parathyroid deficiency, nutritional disturbances, and alkalosis. Most cases met with in this country have nothing to do with the parathyroids. The diagnosis of

parathyroid tetany is easy when the syndrome arises after a subtotal thyroidectomy. Spontaneous parathyroid tetany is to be recognized by the gradual onset of carpopedal spasm associated with a low serum calcium and a high plasma phosphorus. Three disturbances of nutrition may produce tetany—namely, rickets, osteomalacia, and idiopathic steatorrhoea. In rickets and osteomalacia characteristic changes in the bones are present, and in idiopathic steatorrhoea the patient passes large fatty stools. The serum calcium is low owing to defective absorption. The plasma phosphorus, instead of being high as in parathyroid tetany, is low. A large number of cases of tetany are due to alkalosis. In these the serum calcium is normal, but there is thought to be a decrease in available calcium ions. Attacks are usually of short duration, although they may be recurrent. Three types are recognized, and may be diagnosed because of the associated symptoms.

1. Following upon over-breathing and rapid removal of carbon dioxide: this may arise after emotional shock, in hysteria, and in disease of the upper respiratory tract. It is the commonest form of tetany met with in this country.

2. In pyloric or high intestinal obstruction following upon repeated vomiting, with loss of hydrochloric acid, dehydration, and alkalosis.

3. After overdosage with alkalis, especially in the treatment of pyelitis and chronic gastric ulcer.

Treatment of Parathyroid Tetany

Where the blood supply of the parathyroids has been damaged during an extensive thyroid operation post-operative tetany may occur in an acute form and complete recovery may take place even without treatment. It is the chronic form which may be serious. The patient should be given a diet of moderately low phosphate content, meat, yolk of egg, and milk being allowed only once a day. Often this diet must be supplemented by calcium salts. Calcium lactate can be given with the food in doses up to 60 grains six times daily. The equivalent dose of calcium chloride is 30 grains. Being potentially an acid salt it is more effective in relieving tetany than is calcium lactate or calcium gluconate, which have, however, the advantage that they are less apt to upset the stomach. Many patients are almost completely relieved by calcium administration, which forms the basis of all treatment.

In some cases the dose of calcium lactate or chloride may be reduced while the patient continues on a low phosphate diet. In others, while large amounts of calcium salts are taken, it may be necessary to give calcium chloride intravenously or to employ parathyroid extract from time to time. In a severe attack of tetany the intravenous administration of 20 c.cm. of a 5 per cent. solution of calcium chloride relieves symptoms in a few minutes. It is an excellent emergency measure. The solution must be injected slowly, and care must be taken that none of it escapes into the subcutaneous tissues, for necrosis and ulceration may result. The patient feels a sense of warmth all over the skin while the calcium chloride is being given. The muscles in spasm relax, paraesthesiae disappear, and a feeling of greater well-being returns. Although the serum calcium again quickly falls to a low level, the patient will commonly feel fairly well and free from tetany for hours and even days afterwards. If spasms recur the injection should be repeated.

Finally there are cases where so much parathyroid tissue has been damaged or destroyed that the use of the hormone is essential. It is best to inject 30 units of parathyroid extract intramuscularly, repeating the dose

up to twice or even four times daily. At the same time calcium lactate should be given by mouth. In emergency such treatment, because of its slower effect, is not so valuable as the intravenous administration of calcium chloride. But since the blood calcium may remain raised for twenty hours after a single injection of parathyroid extract, it is valuable treatment when severe tetany recurs frequently. Its use should always be controlled by estimation of the serum calcium. Parathyroid extract is an unsatisfactory therapeutic agent, to say nothing of its cost. When administered over long periods of time it may become quite inert, and when this appears it may be impossible to save the patient. In such a case vitamin D should be given in the form of calciferol, of which very large doses may be prescribed. One patient received more than 30 million units in fifty days, and showed no trace of ill effect. There was prolonged benefit, and the blood calcium remained normal for the next three months without any further treatment. A fraction of irradiated ergosterol called A.T.10 has also proved valuable in treatment. This fraction does not contain the anti-rachitic factor, but resembles vitamin D in having the specific effect of raising the calcium content of the serum. The mode of action of this substance is not quite clear, but its effect, though slow in developing, appears to be prolonged. Doses as large as 5 c.cm. on alternate days have been taken by mouth. Manufacturing firms put A.T.10 only at the disposal of clinicians who are able to have serum calcium estimations done regularly, for overdosage may lead to a dangerous hypercalcaemia with metastatic calcification of certain organs. Parathyroid grafting is of no value, even though homoplastic transplants be employed.

If there is hypothyroidism thyroid extract should be prescribed in adequate amounts, usually 2 or 3 grains a day. It is important that the patient be kept in the best possible state of mental and physical health. Malnutrition, infection, fatigue, worry, unhappiness, all aggravate the condition. If foci of infection are found they should be removed when possible. Patients with tetany need interest, increased rest in a quiet environment, adequate sleep, and encouragement to continue at work. There is a tendency for the patient to become introspective, discouraged, and entirely without hope. Active interest and encouragement on the part of the physician does much to prevent and relieve such mental states, and the occasional use of small doses of luminal will help. Perhaps the commonest error in the treatment of tetany is to mystify and frighten the patient and relatives by regarding the condition as grave merely because it is uncommon. In 1861 Armand Trousseau wrote: "This complaint is in general of no gravity, although it sometimes frightens the patients who suffer from it and misleads medical men who do not recognize it."

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(To be continued)

Dr. D. H. Geffen of Enfield has been elected chairman of council of the National Federation of Personal Health Associations. The annual meeting and conference of the Federation will be held at British Medical Association House, Tavistock Square, W.C., on Thursday, June 24.

RADIOTHERAPEUTIC DEPARTMENTS IN GENERAL HOSPITALS

MINISTRY OF HEALTH MEMORANDUM

The Ministry of Health has published this week a short memorandum—the seventy-ninth of its series of reports on public health and medical subjects—on the provision of radiotherapeutic departments in general hospitals.¹ Sir Arthur MacNalty in a prefatory note states that it was a consideration of the extent to which the existing radium centres supply the needs of the country that suggested the memorandum. It is clear, he adds, that much of the population is still indifferently served in this respect, especially in areas which lack voluntary general hospitals suitable for the maintenance of a treatment centre.

The memorandum, which is written by Lieut.-Colonel A. B. Smallman, a medical officer of the Ministry, discusses the provision to be made in hospitals which set out to afford adequate treatment of cancer patients. Such treatment, whether operative or radiotherapeutic, requires the resources of a fully equipped hospital, but owing to the characteristics and cost of radium and of x-ray installations and the need for careful clinical observation supported by physical and biological experiment, the addition of radiation as an alternative or supplement to surgery brings with it the necessity of limiting radiation methods to a comparatively small proportion of hospitals.

Economic Size of Hospital for Radiation Facilities

An attempt is made to estimate the number of beds which will ensure full economic use of equipment for the radiation treatment of cancer. In a 100-bed hospital it is considered that about 120 cancer patients will be admitted annually. Of these about 40 per cent. will be affected in those organs, such as the uterus, mouth, skin, and breast, which are most amenable to radiation alone or combined with surgery. Such a hospital would be too small for reasonable use of radiation facilities. A 300-bed hospital intended for what may be called "acute" cases may be expected to receive yearly about 200 cancer patients, affected either in accessible organs or in other situations where irradiation is given with varying degrees of frequency and success, and in such a hospital radiation apparatus would be in full and regular use.

In England and Wales (outside London) twenty-three general voluntary hospitals have 300 or more beds, of which number eleven possess radium on loan from the Radium Commission and ten have their own stocks, and nearly all of them have deep x-ray therapy apparatus. Of eleven hospitals with 250 to 300 beds, three have radium on loan and five have their own stocks of less than 1½ gramme; four have deep x-ray apparatus. A number of smaller hospitals have supplies of radium of varying and sometimes quite inadequate amounts.

From the experience of hospitals with about 300 beds it appears that the necessary radiation equipment should consist of about 1 gramme of radium and two or three deep x-ray therapy tubes working at 200 to 250 kilovolts. The choice of radium containers is best left to the clinician concerned, and the nature and disposal of the x-ray equipment will again depend upon the views and experience of the officer in charge. With the most

¹ *Cancer: Memorandum on Provision of Radiotherapeutic Departments in General Hospitals.* By A. B. Smallman, C.B.E., D.S.O., M.D. H.M. Stationery Office. (7d. net.)