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Hyperparathyroidism: retrospect and prospect

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Summary

The history of hyperparathyroidism is outlined and the diagnosis and treatment of its various causes reviewed with reference to a series of 153 patients operated on for hyperparathyroidism in the past 20 years. In 119 cases the condition was primary, being due to a tumour or hyperplasia. Future developments in this field are briefly considered.

Introduction

Cecil Joll (Fig. 1), whom we honour this evening, was a most distinguished Fellow of this College and for my generation his name is synonymous with the surgical treatment of thyroid disorders. His book on the thyroid gland[1] was a landmark in the understanding of thyroid function in health and disease and he was a pioneer in the field of thyroiditis[2]. His technical skill is still a legend, and in spirit he continues to preside over our endeavours in the operating theatre on account of the excellent retractor for neck exposure which bears his name (Fig. 2). We are honoured by the presence this evening of Mrs Joll, and those of you who dine here will have seen the lovely gold cup (Fig. 3), once the property of William Cheselden, which was presented to the College by Mrs Joll. I am most appreciative of the honour of being asked to give the Joll Lecture but very humbled, especially when I read the roll-call of those who have preceded me, including as it does Lahey, Dunhill, and Keynes.

The subject I have chosen to talk about this evening is the parathyroid gland because of my special interest in it during the past 20 years. Surgery of the endocrine system is essentially a team endeavour and I have relied greatly on my colleagues at Hammersmith, particularly in the fields of endocrinology, gastroenterology, chemical and histopathology, and radiology. However, it is to the young assistants who have come to work with me that I owe most. They have come not only from Britain but often from overseas and their questions and the subsequent endeavours to answer them have been responsible for much that I shall relate. I wish to acknowledge my debt to them here.

Retrospect

History On 24th May 1834 the Zoological Society of London purchased its first Great

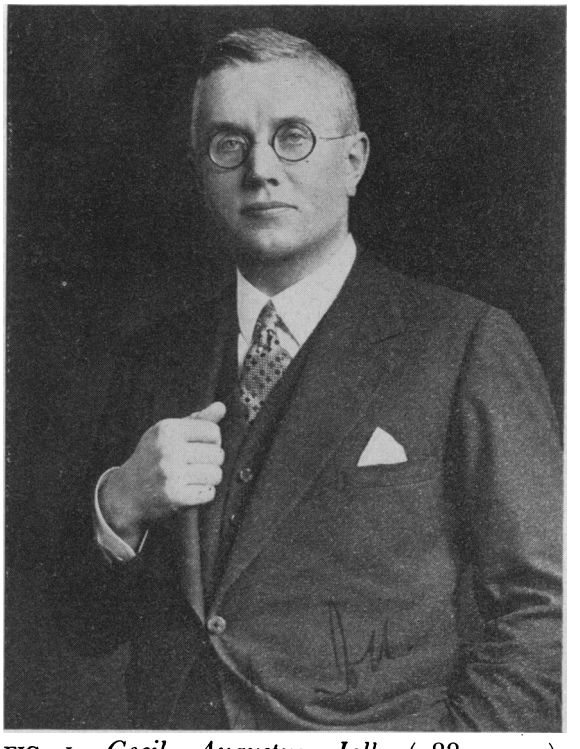


FIG. 1 *Cecil Augustus Joll* (1885–1945), *Surgeon to the Royal Free Hospital, Royal Cancer Hospital, and Miller General Hospital, Greenwich. Member of Council, RCS,* 1939–45.

Cecil Joll lecture delivered on 9th October 1975.

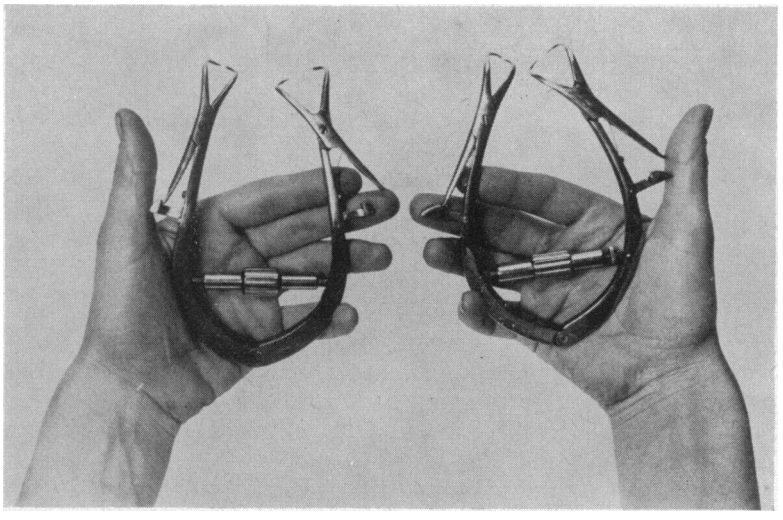
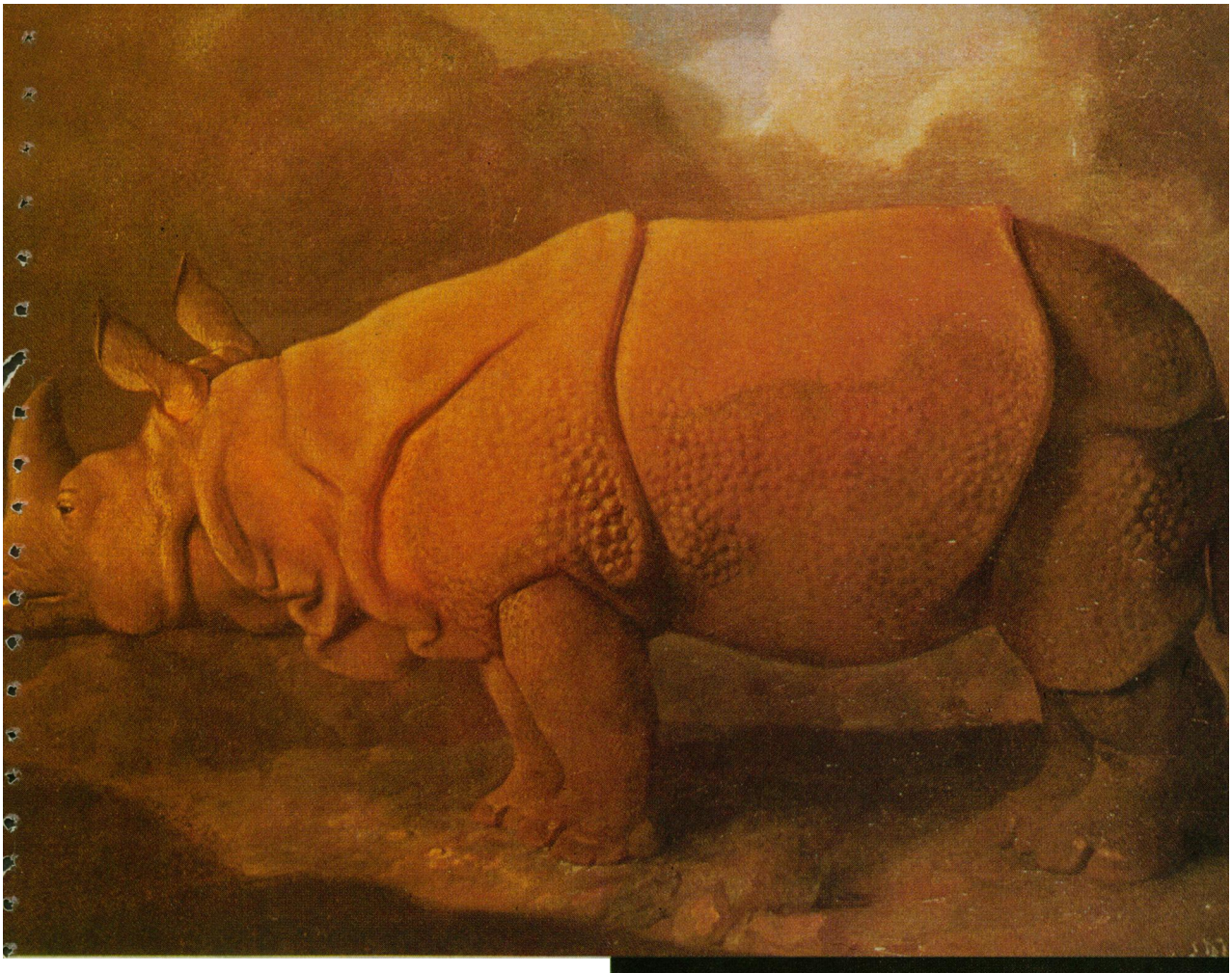


FIG. 2 *Joll's thyroid wound retractors.*

Indian Rhinoceros, *Rhinoceros unicornis;* the commoner African one has two horns. It duly arrived at the Zoo on 20th September and was a great attraction until it died 15 years later on 19th November 1849. Stubbs's magnificent painting of a rhinoceros (Fig. 4), one of the College's great treasures, hangs upstairs in the Hunterian Museum. The Conservator of the Hunterian Museum of this College at that time was Richard Owen (Fig. 5) and he was offered the carcase, which he anatomized; he subsequently read a paper about it to the Zoological Society of London and it was published in their *Transactions*[3]. It is in this paper that the first description of the parathyroid gland appears and I shall quote it: 'A small compact yellow glandular body was attached to the thyroid at the point where the veins emerge'.

Now in the year in which Richard Owen presented his paper to the Zoological Society there was born in Sweden one Sandström (Fig. 6), who in 1880[4] at an international conference in Stockholm presented a paper describing, as he believed for the first time, the glands, which he named parathyroid, in man, horse, rabbit, and cat. To quote from his paper: 'The existence of a hitherto unknown gland in animals that have so often been a subject of anatomical examination called for a thorough approach to the region around the thyroid gland even in man. Although the probability of finding something hitherto unrecognized seemed so small that it was exclusively with the purpose of completing the investigations, rather than with the hope of finding something new, that I began a careful examination of this region. So much the greater was my astonishment therefore when, in the first individual examined, I found on both sides at the inferior border of the thyroid gland an organ of the size of a small pea, which, judging from its exterior, did not appear to be a lymph gland, nor an accessory thyroid gland, and upon histological examination showed a rather peculiar structure'. The structure of the parathyroid continued to appear 'peculiar'. Sir Geoffrey Keynes[5] recalls that in 1927 he worked with Sir Thomas Dunhill on this subject and showed Sir James Berry, that doyen of thyroid surgeons, a section of parathyroid under the microscope. His only comment was: 'I don't believe it'.

The unravelling of the mystery of the function of the parathyroid gland engaged the attention of many scientists in the next 50 years. So small are the glands and so closely applied to the thyroid that for long the effects of their removal were attributed to removal of the thyroid gland. It was Gley[6] (Fig. 7) who was the first to show that it was removal of the parathyroids and not of the thyroid that caused the twitching of tetany in dogs. The basic functions of parathyroid hormone having been defined, the next 50 years have not altered these; in brief, the hormone mobilizes calcium from beneath the periosteum and produces a rise in the blood level of calcium, which is excreted through the kidneys. A concomit-



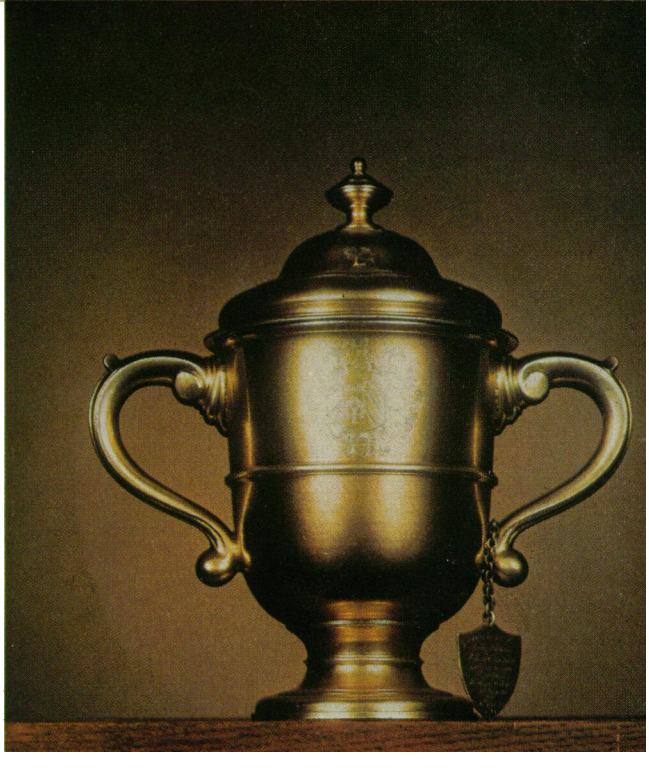


FIG. 3 (*right*) *The Cheselden Cup owned by William Cheselden* FRS (1688–1752), *surgeon and anatomist to St Thomas's, St George's, and Chelsea Hospitals and Warden of the Barber Surgeons Company at the time of separation of Barbers and Surgeons. Gift of Mrs Joll to the Royal College of Surgeons.*

FIG. 4 (*above*) *The Great Indian Rhinoceros* (Rhinoceros unicornis). *This painting by George Stubbs* (1724–1806) *was commissioned by John Hunter and hangs in the Hunterian Museum of the College.*

FIG. 5 *Sir Richard Owen* FRS (1804–92), *naturalist and anatomist, Conservator of the Hunterian Museum, RCS.*

ant lowering of the phosphate in the serum is inevitable unless the kidney has been damaged. The manner in which this knowledge has been translated to the treatment of the disease in man makes interesting reading.

Erdheim (Fig. 8) in 1907[7] noted the relationship of the function of these glands to the structure of the bones and teeth, but von Recklinghausen (Fig. 9), in giving his masterly description of osteitis fibrosa (the name still given to the skeletal changes in this disease)[8], had no idea that an excess of parathyroid secretion was the cause. However, by 1925 both Hanson[9] and Collip[10] had made an extract of the glands which was effective when injected into animals, but 1925 is a memorable year in parathyroid history for another reason since it saw the first successful operation on a patient with parathyroid disease. The story is worth relating.

Albert was a streetcar conductor in Vienna who had been invalided from the army in the 1914–18 war with tuberculosis. In 1921 he began to suffer bone pain and felt tired, and so severe was his disability that he was pensioned. In 1923 X-ray studies revealed decalcified bones and the diagnosis of osteitis fibrosa was made. At that time it was believed that the finding of large parathyroid glands in patients with this disease was due to compensatory hyperplasia and so Albert was given parathyroid extract. His condition worsened and his attending surgeon, Mandl, transplanted parathyroids into him taken freshly from the body of a man who had died after a street accident. Still the condition worsened and Mandl then explored Albert's neck, found a parathyroid tumour, and removed it. His patient showed a remarkable improvement; the calcium disappeared from his urine and his bones recalcified. It is sad to record, though of particular interest with regard to

FIG. 6 *Ivan Victor Sandström* (1852–89), *anatomist at Uppsala, Sweden.*

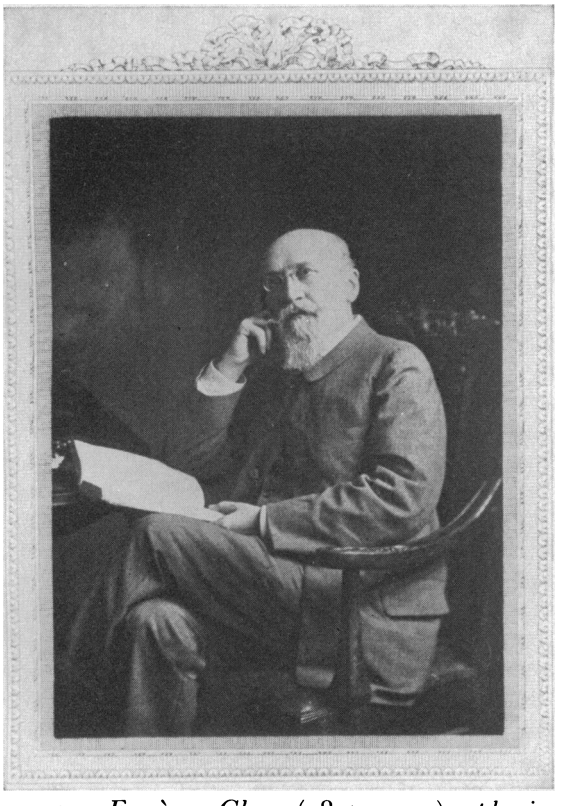


FIG. 7 *Eugène Gley* (1857–1930), *physiologist at the Collège de France, Paris.*

what I shall say later, that 4 years after this the condition returned and proved fatal.

It seems appropriate at this point to mention Captain Charles Martell (Fig. 10), who is certainly the most famous example of hyperparathyroidism because of Fuller Albright's[11] wonderful account which he gave when President of the American Society for Endocrinology. Martell was an officer in the United States Navy in the 1914–18 war and by 1919 his fellow officers noted that he was becoming pigeon-chested. He himself was not well, passed gravel in his urine, and after a slight injury one of his knees collapsed. A few months later, back on duty, his other knee gave way—as Albright said, 'one certainly gets the impression that there was something fundamentally wrong with the structure of the Captain's underpinnings'. Martell came under the care of a metabolic physician, duBois, who found that his blood calcium level was elevated and that his calcium excretion was greater than his intake. At the Massachusetts General Hospital in Boston, where I was first introduced to parathyroid disease, Drs Churchill and Cope searched on six occasions in the operating theatre for a parathyroid tumour without success. On the seventh, after splitting the sternum, they found and removed it, but it was too late: Captain Martell died but certainly not in vain, for the information his case history provided has contributed more than any other to our knowledge of the disease. Lest you should think this could not happen today Figure 11 shows a young Italian plumber before and after the disease had taken hold. He is greatly improved since parathyroidectomy, and my colleagues have reconstructed his jaw.

Materials The basis for my contribution to the subject of hyperparathyroidism this evening is a group of 153 patients upon whom I have operated for this condition in the past 20 years. A number of these were treated because of secondary hyperparathyroidism due to intestinal malabsorption or kidney failure, many

FIG. 8 *Jakob Erdheim* (1874–1937), *morbid anatomist in Vienna.*

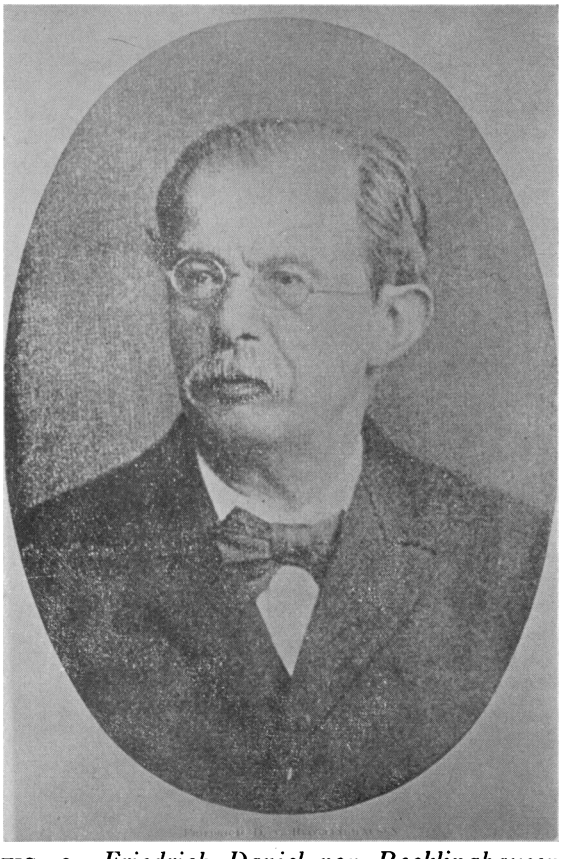


FIG. 9 *Friedrich Daniel von Recklinghausen (1833–1910), pathologist in Strasbourg.*

of these awaiting renal transplantation. If we exclude these a group of 119 is left who have been operated on for primary hyperparathyroidism. These patients have been carefully followed up ever since operation; some have died; those who live overseas have been willing to send details of investigations and it is a tribute to their cooperation and the pertinacity of my assistants that so few individuals have been lost to follow-up. The pattern of sex and age at presentation is shown in Figure 12.

Methods The problems of diagnosing hyperparathyroidism have been written about so much and so often that I will not attempt to review them. However, for the diagnosis to be considered the serum calcium should at some time be elevated and those conditions excluded which are also likely to elevate it, such as malignant disease, the taking of vitamin D, sarcoidosis, thyrotoxicosis, and, rarely in this country, the milk–alkali syndrome. The surgeon's problem then is how to locate the tumour or tumours and the solution to this problem remains basically the same today as it was 40 years ago when the principles were clearly stated by the pioneers, especially Oliver Cope[12].

What are they? A well-conceived operation with wide exposure of the neck, meticulous haemostasis to avoid staining of the tissues, and the eventual recognition of the tumour by its golden tan colour and its vascularity, which makes it so prone to bruising. All four parathyroids should be identified before any tissue is excised. In their embryological development from the 3rd and 4th branchial clefts the parathyroids, even in the normal individual. migrate so that the 4th pair lie higher in the neck than the 3rd and, deriving their blood supply from the thyroid beneath whose capsule they lie, they are not easy to locate. Although the majority of parathyroids, both normal and abnormal, lie in relation to the lower pole of the thyroid gland, aberrations in their migration have led to their eventual discovery in every sort of situation from the base of the

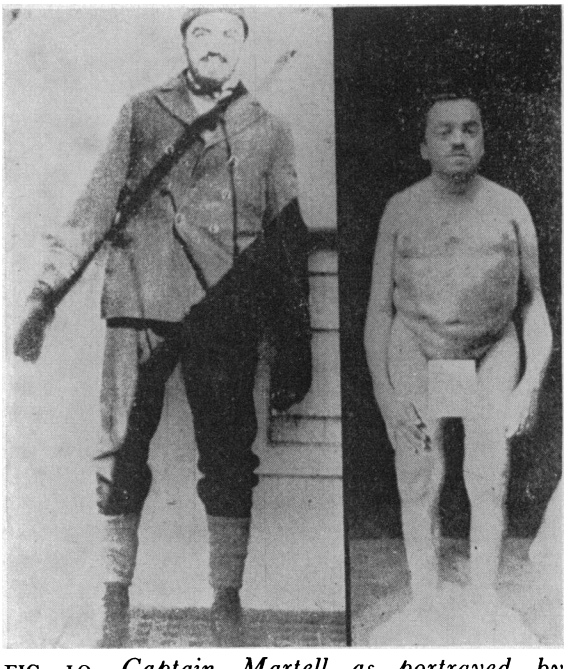


FIG. 10 *Captain Martell as portrayed by Fuller Albright before and after the onset of hyperparathyroidism.*

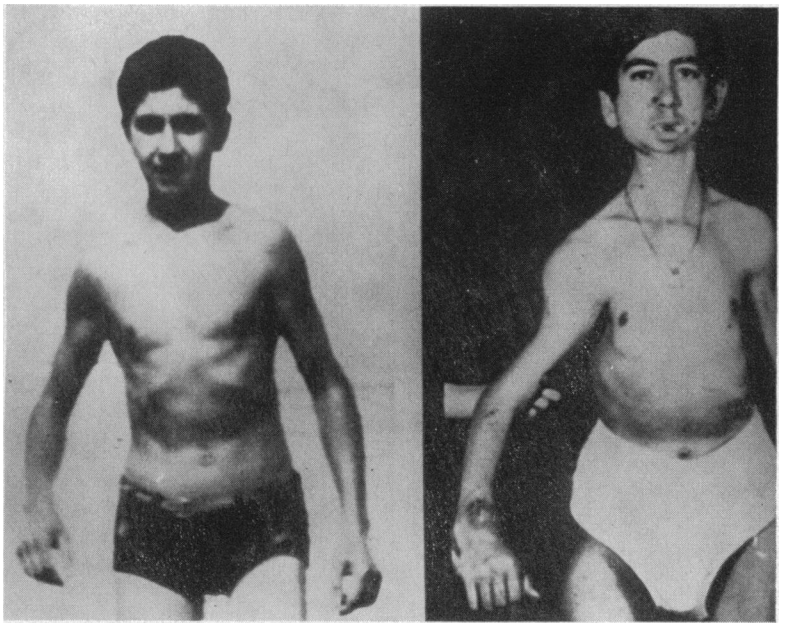


FIG. 11 *Author's patient before and after onset of hyperparathyroidism.*

skull above to the upper mediastinum below and from the carotid sheath laterally to behind the oesophagus in the midline. To add to the confusion there may be five and rarely six parathyroid glands present.

How useful it would be if we had some satisfactory method of locating these tiny glands! A parathyroid adenoma is rarely palpable clinically—only two in this series. A barium swallow may show a tell-tale indentation of the oesophagus and in my hands is a routine which has proved helpful in 10% of cases. Cineradiography has not improved these results. Arteriography has something to offer but, since it is not without hazard, should not be adopted routinely. Professor Aird[13] first drew attention to the technique of localized arteriography for this purpose in the neck, but it has not proved satisfactory. Arch aortography in the hands of my colleague Professor Steiner has been occasionally very useful, demonstrating a tumour blush.

There has been a recent wave of enthusiasm for using toluidine blue intravenously to stain the glands[14]. After a trial I have found it easier to recognize the brownish yellow colour of the unstained tumour rather than when it is coloured blue. In addition, toluidine blue can cause arrhythmia and cardiac arrest, which limits its usefulness. More recently methylene blue has been proposed by Dudley[15]; it is nontoxic and confers a slatey blue colour. American workers[16] claim that methylene blue stains abnormal glands more than the normal ones. Again I have to say that I have not adopted dye technique routinely and believe that if a parathyroid gland is in view it can be recognized, and if it is not in view any colour change is immaterial.

Radioactive localization has been a failure in our hands and in those of many other workers. Selenium-labelled methionine, which has generally been used, is not specific for parathyroid tissue and gives false positives.

However, it is now possible to obtain good localization by selective venous catheterization[17]. The catheter is introduced into a femoral vein and passed through the inferior vena cava and right heart to the mediastinum and neck veins. The location of the tip of the catheter is confirmed by injection of diodone and a blood sample is then taken and a radioimmunoassay of parathyroid hormone performed. Twenty or 30 samples may be taken and a typical result is shown in the table, which reveals a high level in the upper left area. This patient had an adenoma removed from this site after three previous explorations had failed. The technique is not without morbidity and on one occasion it was not helpful because

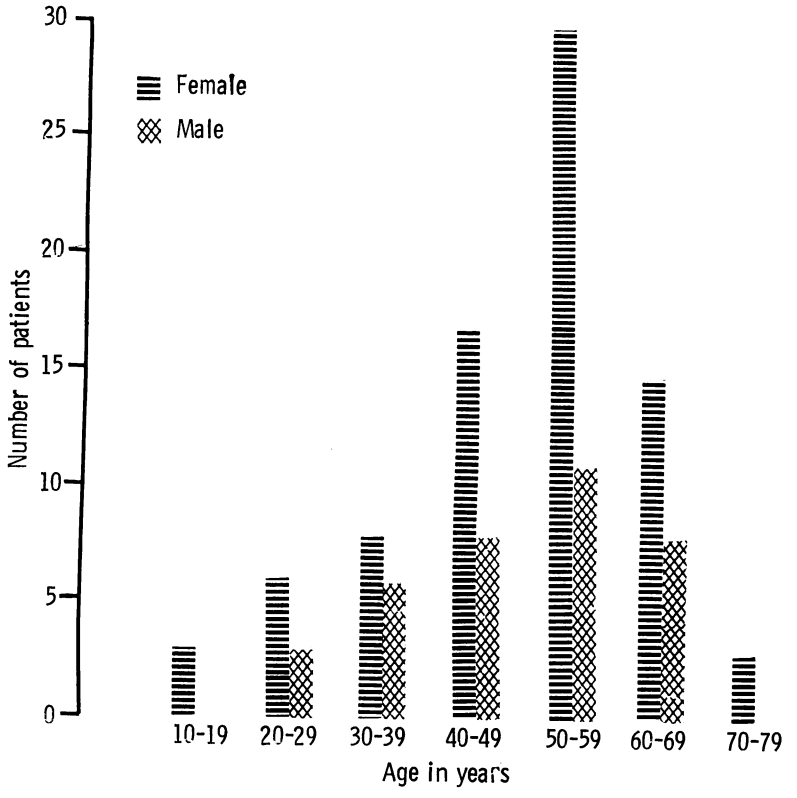


FIG. 12 *Age and sex of* 122 *patients operated on for primary hyperparathyroidism.*

the parathyroid hormone levels were uniformly high throughout the neck so that localization was not possible. I reserve this technique for patients who have had a previously unsuccessful operation. To digress for a moment, the radioimmunoassay of parathyroid hormone (PTH), which should have been of great diagnostic value in this disease, is not yet particularly reliable. The PTH molecule is a complicated chain of amino acids and although only a particular fragment of it appears to be biologically active, this is not the part of the molecule which is immunoreactive. In addition it takes many days to carry out the assay, introducing a delay of something like 2 weeks between the investigation and operation.

The single tumour In the 20 years under review 122 patients were operated on for primary hyperparathyroidism and if we exclude 20 who were followed up for less than one year, although these were all normocalcaemic after operation, there remain 102. Of these, 11 had been previously operated on elsewhere and were referred because of persistent or recurrent hypercalcaemia.

The tissue removed at operation has been reviewed and the diagnosis defined as *adenoma* if only one gland was enlarged and *hyperplasia* if more than one gland showed increased cellularity, whether nodular or diffuse. Of the 102 patients, 73 had a single adenoma, 26 had hyperplasia, and in 3 the tumour was carcinomatous.

Looking at the 73 patients with a single adenoma first, they were treated by complete removal of the tumour and nothing else other than biopsy of one or, latterly, all the other parathyroids. Biopsy of a normal parathyroid can be performed by removal of a really minute sliver of gland, so small that it is unsuitable for cryostat review and must be embedded in paraffin wax before sectioning. All bar one of these patients has had a complete remission

Selective venous catheterization and venous hormone immunoassay. Male aged 44. (For key see Fig. 13)

Position	*Immunoreactive parathyroid hormone (μg/l)*
1 Left internal jugular high	1.85
2 Left internal jugular mid	1.85
3 Left internal jugular low	0.33
4 Left internal jugular lowest	< 0.15
5 Left subclavian	,,
6 Innominate	,,
7 Innominate–caval junction	,,
8 Right paravertebral	,,
9 Right subclavian–jugular junction	0.64
10 Right internal jugular high	0.26
11 Right internal jugular mid	< 0.15
12 Right internal jugular low	,,
13 Right subclavian–jugular junction	0.21
14 Right subclavian	< 0.15
15 High superior vena cava	,,
16 Low superior vena cava	,,
17 Inferior vena cava below hepatic veins	,,
18 Azygos	,,

Note highest hormone levels in upper left jugular vein suggestive of tumour in this location.

of hypercalcaemia and its attendant symptoms. The one exception was a patient in whom no tumour was found but four parathyroids were biopsied and reported normal. She is now normocalcaemic. Three patients from early in this study have developed hypocalcaemia and require replacement therapy. They all had a simultaneous partial thyroidectomy and it seems likely that normal parathyroids were removed.

The excellent results in these 73 patients who had as sole treatment the removal of the single adenoma is at variance with reports of some other workers in the field, in particular Ballinger[19] and Paloyan[20]. The latter recommends subtotal parathyroidectomy in his patients but does report an incidence of 8% permanent hypoparathyroidism.

Hyperplasia and multiple tumours Regularly when exploring a patient's neck for parathyroid disease all four glands are found to be enlarged and the pathologist reports hyperplasia on frozen section of a biopsy specimen. More rarely two or three glands are enlarged, usually by adenoma or nodular hyperplasia. Twenty-six patients in this series (21%) showed hyperplasia of more than one parathyroid gland; 18 eventually had all four glands involved.

My policy has been the same as that recently reported by Wang[18] of removing parathyroid tissue commensurate with the severity of the disease and the size of the glands. In severe hyperparathyroidism three glands and half of another were removed; in less severe cases one or two of the larger glands were excised and the others biopsied. The positions of the identified and remaining glands were marked with silver clips and black silk sutures so that they could be located if exploration was called for in the future. This group of patients with multiple parathyroid involvement has proved to be the most demanding in treatment and has been associated with abnormalities of other parts of the endocrine system and of the pa-

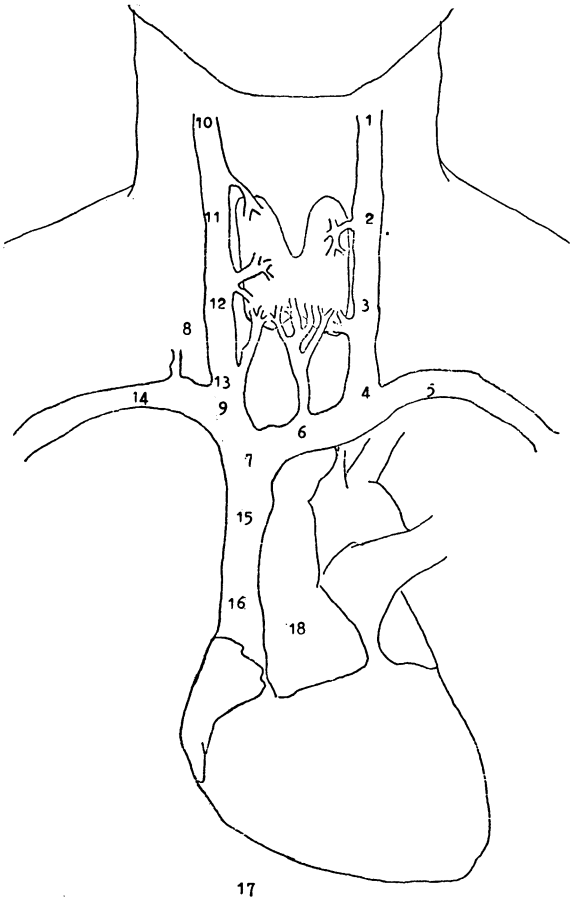


FIG. 13 *Key to table, showing positions of venous hormone assay.*

tient in general. One particularly fascinating and unexplained observation was made by Orlo Clark[21] when working with me and that was that all patients who had cysts of the jaws—a well-known sign of severe hyperparathyroidism—had involvement of all four parathyroid glands.

Multiple endocrine adenomatosis When Langdon-Brown[22] in the early 'thirties described the various endocrine glands as members of the endocrine orchestra with the pituitary as their leader he was drawing attention to the amazingly close integration of the hormone-producing glands. Hormones provided the early means of communication in the body and were superseded in speed by the evolution of the central nervous system. (It is not surprising that many of the endocrine glands, Pearse's[23] APUD series, should have developed from tissue beside the neural crest which he has so elegantly demonstrated with his histochemical techniques.) From time to time a patient presents who has tumours in two or more endocrine glands, as first described in a group of eight patients at the Mayo Clinic by Underdahl[24]. This distinctive syndrome, with tumours or hyperplasia in the parathyroids, pituitary, pancreas, and adrenal cortex in that order of frequency, was further investigated by Wermer[25] and demonstrated by Steiner[26] to be a familial syndrome transmitted as an autosomal dominant with varying penetrance. He called it 'multiple endocrine adenomatosis' and it is usually referred to as MEA I to distinguish it from another group, MEA II, in which the adrenal medulla and the C cells of the thyroid are involved.

The parathyroids are the glands most often involved in MEA I, and others working in this field[27-30] have reported an incidence of 2–7% for coexisting endocrine disorders in primary hyperparathyroidism. In 119 patients operated on at Hammersmith Hospital we found 21 with evidence of MEA I, an incidence of 18%[31]. Why have we found so many more examples than others? Probably because of the careful follow-up, since some patients do not develop overt symptoms of other endocrine disease for years after the initial hyperparathyroidism is discovered. Also because we have been at pains to examine the whole endocrine system, whose integrative action is all-important, and indeed to examine the whole patient.

Is this particular group of patients more at risk than the general run of those with hyperparathyroidism and can they readily be distinguished? To the first question I should answer 'yes', disagreeing with Purnell[32], who believes the disorder runs an indolent course and advises a wait-and-see policy. To the latter question I would reply that there is no royal road to the diagnosis of MEA I. Here are the facts. There were 17 females and 4 males and the mean age at diagnosis was 49, which is indeed less than that for our so-called uncomplicated primary hyperparathyroid patients. Seventeen presented with hypercalcaemia, but only 11 had symptoms related to it. The 4 who presented with other endocrine diseases and were only later discovered to be hypercalcaemic comprised 3 acromegalics, one of whom also had hypoglycaemic attacks, and a fourth patient who had Cushing's disease.

You may well begin to think, as I did at this stage, that if a patient has hyperparathyroidism he either has one tumour, following excision of which he is virtually cured, or he has hyperplasia of all four glands. This hyperplasia may be initially confined to one gland and in some instances, by being nodular in pattern, resembles an adenoma, but with the passage of time it is likely that all four glands will be involved. This over-simplified account is not entirely supported by facts, but it is true that if other endocrine glands are involved, as in MEA I, then the parathyroids are more likely to show hyperplasia than a single adenoma.

We have recently looked at this problem from another angle. Plasma gastrin levels are sometimes raised in hyperparathyroidism, and after parathyroidectomy they usually fall except in patients with the Zollinger–Ellison syndrome and those with achlorhydria[33]. We have studied a group of our hyperparathyroid patients postoperatively, measuring their fasting gastrin and comparing them with controls matched for sex and age. I have to acknowledge the cooperation of our nursing staff, matron included, and others, including the Hospital Friends, in this investigation. Excluding hypochlorhydrics, there were 42 postparathyroidectomy patients (with a mean of 6 years after operation) and 34 controls. The mean fasting gastrin level in the patients with aden-

oma was similar to that in the controls, but in patients with hyperplasia the level was significantly higher ($P < 0.001$). This may in future provide a useful test for distinguishing patients with parathyroid adenoma from those with hyperplasia and additionally supports the thesis that the latter group present with hypercalcaemia as only one facet of multiple endocrine adenomatosis.

Prospect

What of the future? Hyperparathyroidism is a relatively common condition and routine biochemical screening of patients is going to reveal many examples, so that parathyroidectomy will be in increasing demand[34]. There appears to be no justification for a wait-and-see policy since renal damage is insidious in onset and rarely, if ever, reversible.

Fortunately the prospects in the treatment of this disease are good because a carefully planned operation showed that 80% of our patients had a single adenoma, after removal of which they remained fit and well, often for many years. However, 20%, and we are not yet sure which 20%, are at risk from further disease which may develop at any time: recurrent hyperparathyroidism and overactivity of pituitary, pancreas, and adrenal of MEA I type. Again it is fortunate that not all patients will show evidence of this.

Thus until we know more about this fascinating condition we must continue to follow the progress of our patients indefinitely.

The portraits of Sandström and Gley are reproduced by courtesy of the Wellcome Foundation and that of von Recklinghausen by courtesy of the Froben Press of New York City.

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