PARATHYROID ADENOMA

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Full blown hyperparathyroidism with osteitis fibrosa cystica is relatively easy to diagnose and if a palpable tumour is present, equally easy to cure by surgery. It is becoming increasingly evident, however, that many patients with occult parathyroid adenomas and no osseous changes have gone undiagnosed and thus suffered needless disability. A high index of suspicion and knowledge of newer screening techniques for discovering hyperparathyroidism will frequently uncover such patients whose disease may be curable by surgical means.

The purpose of this paper is to review the techniques used to diagnose an occult parathyroid adenoma and to emphasise the surgical technique employed for its location and removal. Four cases in our recent experience serve as illustrations.

ILLUSTRATIVE CASES

Case 1. A 54 year old Chinese housewife presented with a history of two years of epigastric pain occurring soon after meals and associated with vomiting. In addition she had increasing weakness of the limbs over the last year. She was unable to walk and had suffered from marked loss of weight and anorexia. There was an increased frequency of micturition both during the day and night (formerly $\frac{D}{N} = \frac{2-3}{0-1}$ and now $\frac{4-5}{2-3}$).

Clinically she was a small woman, pale and wasted, lying still in bed. Her bones were generally tender, particularly those of the lower limbs which were very weak and wasted. A firm nodule 1" x 1½" was felt in the suprasternal notch. Blood pressure was 150/100. Her cardiovascular and respiratory systems were normal.

Barium meal X-ray of the alimentary tract was reported as normal. The bones showed extreme decalcification with very coarse trabeculation of the bone pattern in the pelvis giving the impression of large cystic areas in the ilia. The bones of the skull had a thickened granular appearance. The phalanges showed erosion in the proximal areas. Rarefied areas were seen in the lower radii and ulnae. Teeth showed absence of the lamina dura in all elements. There was much rarefaction of the ribs some of which showed localised expansion. There were no kidney stones.

Biochemical Investigations. Serum Calcium 15.0 mgm.% and Inorganic Phosphate 2.5 mgm.%. Sulkowitch's test for calcium in the urine showed a heavy precipitate indicating excessive urinary concentration of calcium. Alkaline Phosphatase 60 K.A. Units/100 ml.

The patient later developed substrochanteric and subcapitalar fractures of the right femur and a fracture of the right tibia and was under the care of the Orthopaedic Surgeon.

A diagnosis of parathyroid adenoma with osseous changes and pathological fractures was made and on 25th March, 1959 her neck was explored and a parathyroid adenoma removed (Fig. 1).

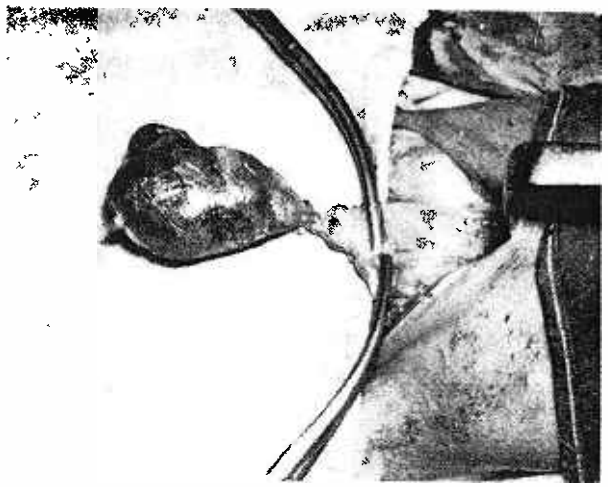

Fig. 1. Adenoma as seen at operation.

Histo-pathology. "An encapsulated tumour consisting of sheets of polygonal cells of fairly uniform appearance. The nuclei are round and hyperchromatic, the cytoplasm markedly vacuolated and clear and cell margins fairly distinct. The tumour is very vascular and the tumour cells display a distinct pseudoglandular arrangement around the numerous thin walled capillaries (Figs. 2 and 3). The structure is characteristic of a Chief Cell Parathyroid Adenoma".

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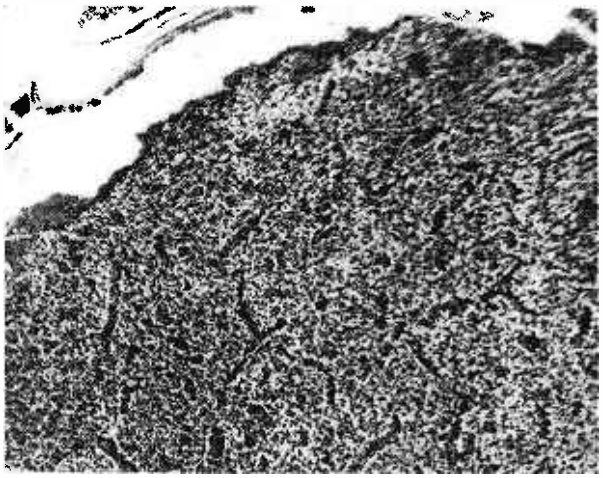

Fig. 2. Microscopic appearance. Low Power.

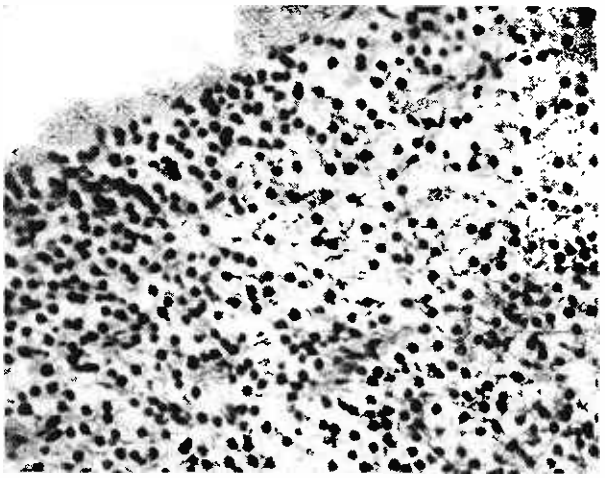

Fig. 3. Microscopic appearance. High Power.

Since August 1959, she has been an out-patient of the Orthopaedic Unit for treatment of her fractured limb. She has otherwise been well with normal appetite and free of bone and epigastric pains. Bowel and micturition habits are now back to normal. She herself feels well and is much stronger and has gained weight.

Comment. This case in which bone pain and decalcification dominate the clinical picture is a characteristic example of the type of hyperparathyroidism described in textbooks. The palpable lump in the neck made the location and subsequent removal of the functioning parathyroid adenoma relatively simple.

Case 2. This 31 year old Indian Tamil had been passing urinary stones almost once a year for the past 19 years. The episodes were associated with haematuria and right renal colic for the five years prior to admission. There had been no gastrointestinal complaints and he drank milk but rarely. The first admission to the Singapore General Hospital was in November 1959 following passage of another renal stone.

Physical examination was essentially normal. No masses were noted in the neck. Blood pressure was 120/80. Haemoglobin was 94%. Chest X-ray was normal. An X-ray of the abdomen revealed multiple stones in the region of both kidneys, with a few stones in the lower end of the right ureter. Intravenous pyelogram showed no function on the right, and hydronephrosis of the left. Blood was seen to emerge from both ureteral orifices at cystoscopy. A right ureterolithotomy was performed on 13th November, 1959 and the patient subsequently discharged.

An intravenous pyelogram performed as an out-patient in January 1960 showed a return of renal function on the right side, but there was bilateral hydronephrosis and one stone at the lower end of the right ureter. Studies between November 1959 and February 1960 revealed serum calcium concentrations varying between 10.8 mgm.% and 11.6 mgm.%. Inorganic Phosphates varied between 2.9 mgm.% and 3.1 mgm.%; blood urea between 20-27 mgm.%; and urine showed a faint precipitate with Sulkowitch's test for calcium. Renal function tests were within normal limits.

He was readmitted to the hospital for definitive study and treatment on February 24th, 1960.

Parathormone activity, as directly measured by the rate of tubular reabsorption of phosphates, was abnormal on five separate occasions. Tubular reabsorption by the method of Goldman et al (1957) was determined as follows:

$$TRP = 1 - \frac{UP \times SC}{UC \times SP}$$

where UP = Urinary Inorganic Phosphate Concentration.

UC = Urinary Creatinine Concentration.

SC = Serum Creatinine Concentration.

SP = Serum Phosphorus Concentration.

Normally 85% of phosphorus is reabsorbed. TRP measurement in this patient on five occasions were 69%; 71%, 72%, 71% and 71%.

On the strength of these findings exploration of his neck was undertaken on March 24th 1960. An adenoma 1 x 2 cm. was found behind the pharynx posterior to the right superior pole of the thyroid gland. The left superior parathyroid gland was slightly larger than normal and was also removed. The two normal inferior parathyroid glands were carefully identified and left in situ.

The patient was given prophylactic calcium and calciferol post-operatively for two days, and his convalescence was uneventful.

Post-operative biochemical data

T.R.P. :

86.5, 88.0 and 89.0%

Serum Calcium :

10.0, 10.2 and 10.1 mgm.%

Serum Inorg. Phosph. :

3.8, 3.5 and 3.2 mgm.%

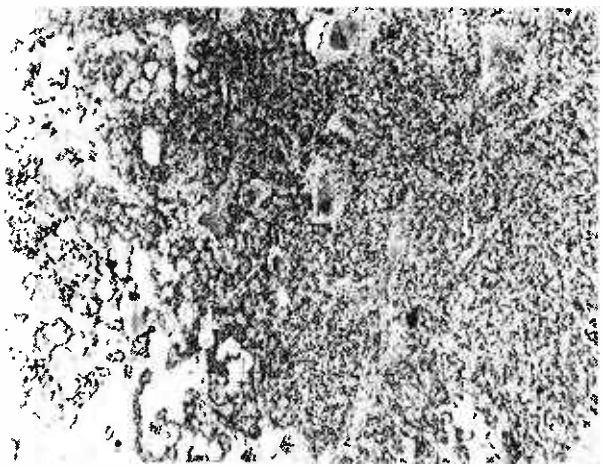

Fig. 4. Rt. Sup. Parathyroid (Adenoma). Low Power.

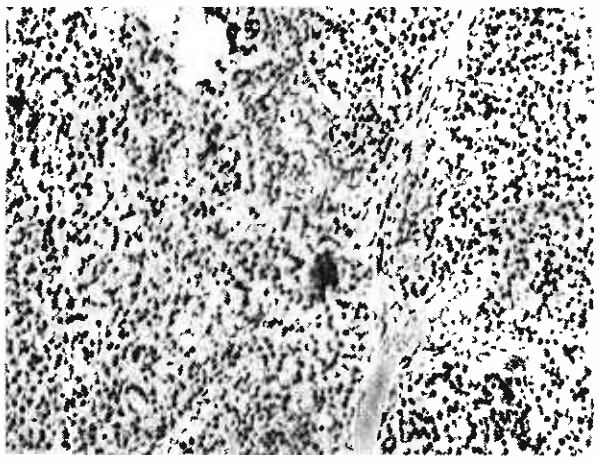

Fig. 5. Rt. Sup. Parathyroid. High Power.

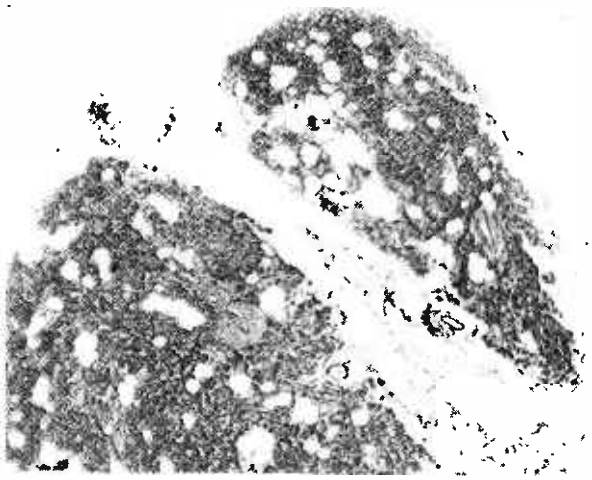

Fig. 6. Lt. Sup. Parathyroid. Low Power.

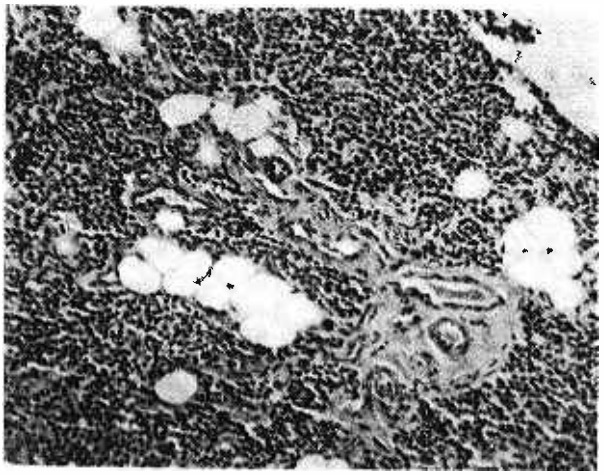

Fig. 7. Lt. Sup. Parathyroid. High Power. The Lt. Sup. Parathyroid shows some degree of hyperplasia.

Histological examination of the parathyroid glands showed a typical Chief Cell benign adenoma of the right parathyroid (Figs. 4 and 5) gland with an occasional large hyperchromatic nucleus. The left superior parathyroid gland showed some hyperplasia, but no definite adenomatous formation (Figs. 6 and 7).

Comment. The diagnosis of hyperparathyroidism was strongly suspected in this man because of multiple renal stones. The serum calcium was persistently on the high side of normal. The abnormal tubular reabsorption of phosphorus (TRP Test) which specifically measures parathormone activity clinched the diagnosis. Despite the absence of a palpable tumour a thorough exploration of the neck uncovered the functioning parathyroid adenoma.

Case 3. This 26 year old male Chinese was first seen in February 1957 with a history of recurrent attacks of left renal colic over the last six months. Radiological investigation revealed bilateral nephrocalcinosis and a large stone in the left ureter with left hydronephrosis. A left uretero-lithotomy was done. Since then he had had repeated attacks of left renal colic and had passed three small stones. In July 1958 he had a right renal colic following which he passed a small stone.

He was well until May 1960 when he came with a left renal colic and haematuria. Full biochemical and radiological investigations were carried out.

His blood pressure was normal — 120/70. Haemoglobin 95%. Blood urea was 24 mgm.%. Renal function tests were within normal limits.

Serum Alkaline Phosphatase was 16 K.A. Units. Urine showed microscopic evidence of

haematuria with urinary calcium of one plus with Sulkowitch's Reagent.

Serum Calcium, Phosphorus and Tubular Reabsorption of Phosphate studies were done.

Findings

Date	T.R.P.	Serum Calcium	Serum Inorganic Phosphate
23.5.60	73.5%	12.4 mgm.%	2.4 mgm.%
24.5.60	76.0%	12.5 mgm.%	2.4 mgm.%
26.5.60	72.8%	12.7 mgm.%	2.6 mgm.%
30.5.60	73.0%	12.4 mgm.%	2.3 mgm.%
31.5.60	71.5%	12.5 mgm.%	2.3 mgm.%

Radiological Investigations

1. **Chest.** Healed fibrotic lesion in the right infraclavicular region.
2. **Skeletal Survey.** No abnormality detected.
3. **I.V.P.** Left renal and ureteric calculi with hydronephrosis.

There was no palpable lump in the neck. There was no relevant past history of peptic ulcer, pancreatitis, polyuria or polydypsia.

With this biochemical evidence of hyperparathyroidism, a cervical exploration was carried out on June 1st, 1960 and a parathyroid adenoma 2 cm. x 1 cm. x 0.5 cm. in size was found behind the left superior pole of the thyroid (Fig. 8). The other three parathyroids were found to be normal in size. Following removal of the adenoma the patient was given prophylactic calcium and calciferol. His post-operative bleeding and clotting times were normal but the prothrombin index dropped to 74% of normal.

Post-operative Biochemical Data

	T.R.P.	Serum Calcium	Serum Inorganic Phosphates
1.	88%	10.0 mgm.%	3.5 mgm.%
2.	86%	10.1 mgm.%	3.6 mgm.%
3.	86%	10.1 mgm.%	3.5 mgm.%

Microscopic examination of the adenoma revealed a typical Chief Cell adenoma with occasional groups of Ozyphil cells and a few scattered Water-clear cells (Figs. 9 and 10).

Comments. This man suffered from repeated attacks of renal colic due to calculi before a parathyroid adenoma was suspected. Although no tumour was palpable, typical biochemical findings justified exploration of the neck with very gratifying results.

Fig. 8. Macroscopic appearance.

Fig. 9. Microscopic appearance. Low Power.

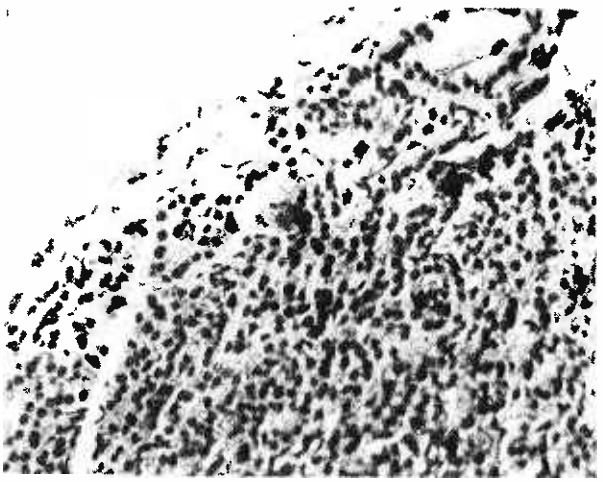

Fig. 10. Microscopic appearance. High Power.

Case 4. A 52 year old male Indian was admitted on two occasions for bilateral renal colic. On examination, he was found to be very obese, B.P. 150/90. A visible rounded mass was found in the region of the left lobe of the thyroid, mea-

suring 3 cm. in diameter, firm and mobile. It moved up and down with deglutition.

Biochemical Data

Serum Calcium :
11.5, 14.4, 14.6 and 15.0 mgm.%.
Serum Inorg. Phosph. :
2.1, 1.9, 1.8 and 2.0 mgm.%.
Alkaline Phosphatase : 18 K.A. Units.
T.R.P. : 76, 68%.
Sulkowitch test : 3+.
Blood urea : 16 mgm.%.

Intravenous Pyelogram. There was gross right hydronephrosis.

In view of the history, and biochemical data, the lump in the neck was diagnosed as an adenoma of the parathyroid, and surgical removal carried out.

Operative Findings

A large cyst, 4 cm. in diameter, was found in the posterior portion of the lower half of the left lobe of the thyroid (Fig. 11). The fluid was a dark grey green in colour and turbid and looked very much like the fluid one finds in a colloid cyst. No separate parathyroid tumour was found but embedded in the lower posterior wall of the cyst was a bean-shaped firm swelling, about 1 cm. long and 5 mm. wide, with a greyish-white cut surface.

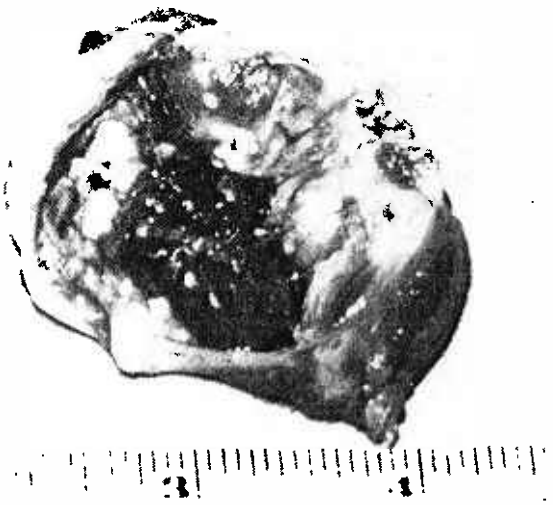

Fig. 11. Parathyroid Cyst opened.

The cyst was excised in toto and frozen sections made of the suspected nodule confirmed it was a parathyroid adenoma.

The right inferior parathyroid was identified and left in situ. Both upper parathyroid glands were not found.

Post-operative

The patient's recovery was uneventful. No attacks of tetany occurred. Calcium tablets were given as a precautionary measure however.

Post-operative Biochemical Data

Serum Calcium :	9.6, 9.7 mgm.%
Serum Inorg. Phosph. :	3.1, 3.1 mgm.%
T.R.P. :	91, 89 and 88%

Histological Report

The cyst was found to be a parathyroid cyst, its wall being composed of clear-cell adenomatous tissue. The presence of cellular pleomorphism and capsular infiltration suggested malignant change.

Comment

The presence of a palpable tumour and its association with unequivocal biochemical data made the pre-operative diagnosis a simple matter. However, the cystic nature of the mass initially caused the impression that it was a colloid cyst of the thyroid, embedded in the wall of which was the parathyroid adenoma.

Biochemical investigations in a series of patients with renal colic produced evidence suggestive of parathyroid tumour in two patients. However, one refused operation and the other elected to go elsewhere for operative treatment.

DISCUSSION WITH REVIEW OF THE LITERATURE

In 1925 Collip made crude parathyroid extracts from bovine glands. Rasmussen (1961) recently isolated a single protein with a molecular weight of approximately 9,500 consisting of a single polypeptide chain. There appear to be at least two distinct actions of the parathyroid hormone — phosphaturic and calcemic.

Mechanism of Action of the Parathyroid Hormone

The calcium ion concentration of the plasma appears to regulate the secretory activity of the parathyroid glands. The adrenal and pancreas, as well as the pituitary, all exert a regulatory effect on the serum phosphate concentration, and this in turn may cause parathyroid enlargement.

Calcium metabolism is mainly regulated in the bone, kidney, gastro-intestinal tract and lactating mammary gland. The hormone may be involved in the transport of calcium across a variety of membranes (intestinal epithelium, renal tubules, bone cells and mammary epithelium) and it is

involved in the turnover of phosphate in the kidney and possibly other organs. The effect on bone is to increase the rate of normally occurring resorptive process. It acts by converting potentially osteogenic cells from osteoblastic into osteolytic cells.

Phosphaturic Action of Parathyroid Hormone

Normally, the renal tubules reabsorb 80 to 90 per cent of the phosphate filtered through the tubules. The assessment of the phosphaturia in clinical practice depends on the determination of the phosphate-creatinine clearance ratio (Cp : Ccr).

$$Cp : Ccr = \frac{\text{Urine phosphate} \times \text{serum creatinine}}{\text{Serum phosphate} \times \text{urine creatinine}}$$

(all in mg./100 ml.).

The resultant figure denotes the proportion of filtered phosphate which is not reabsorbed by the renal tubules (Nordin, 1958). The clearance ratio varies also with the serum phosphate and does not provide adequate information about phosphate excretion. The true relation between the serum phosphate and clearance ratio, as derived from the data of Milne et al (1952) is:

$$Cp : Ccr = 0.64 \times \log \text{serum P} - 0.25 \pm 0.12.$$

It has been suggested that in any given case the observed clearance ratio should be compared with the predicted value for the prevailing time.

Knowing the serum (S) and urine (U) concentrations of phosphate (P) and creatine (C) the Tubular Reabsorption of Phosphate is calculated by the formula.

$$TRP = 1 - \frac{UP \times SC}{UC \times SP}$$

The lowering of the serum phosphate with increased activity of the parathyroid is associated with a lowering of the renal threshold to phosphate produced by a reduction in tubular reabsorption. Conversely, a low, clearance of phosphate by the kidney has been observed in hyperparathyroidism.

Parathyroid Hormone and Calcium Metabolism

At the First International Congress of Endocrinology held at Copenhagen in July 1960 various aspects of parathyroid activity were discussed by eminent authorities on the subject. It was pointed out that hyperparathyroidism is not a rare disease and the physician has to suspect it in general practice and confirm it later by biochemical and radiological means. Finally it has to be localised and surgically verified.

Certain difficulties occur due to the remittent course of the disease and the impaired renal function. In about half the cases single estimations of calcium level in blood and the calcium excretion in the urine were within normal limits. Alkaline phosphatase activity in serum is altered only in cases with bone disease. Tubular reabsorption of phosphates may be inconclusive. However, the increase of citric acid level in serum above 3 mg./100 ml. is of importance. Considerable arteriovenous difference of calcium concentrations is present in many cases.

Gilbert S. Gordon (1960) reviewed the current status of laboratory tests for hyperparathyroidism.

(1) All cases had hypercalcemia; often in mild and borderline cases, it was evoked only by restricting dietary phosphate intakes.

(2) The hypercalcemia of hyperparathyroidism is characterised by normal distribution between protein-bound and unbound moieties.

(3) Serum protein electrophoretic pattern is of diagnostic value, not only in excluding sarcoidosis and myeloma, but in hyperparathyroidism the alpha$_2$ and beta-globulins are uniformly raised.

(4) Renal Phosphate leak is demonstrated by reduced tubular reabsorption of phosphate (TRP) or increased phosphate clearance. It was associated with hypophosphatemia in only 40% of cases. In hyperparathyroidism, TRP is less than the normal 90-95% on 430 mgs. phosphate intake and less than the normal of 75-80% on 3,000 mgs. phosphate diet. Phosphate wasting also occurs in some cases of Sarcoidosis, Myeloma, Debr'e - deToni - Fanconi syndrome, Osteomalacia, Cushing's syndrome and rarely in Pyelonephritis.

(5) Calcium tolerance test is no longer used routinely.

(6) Cortisone test (failure of hypercalcemia to disappear during administration of large doses of corticoids) was diagnostically valuable. Cortisone uniformly abolished the hypercalcemia of thyrotoxicosis, sarcoidosis, vitamin D poisoning and often reduced the hypercalcemia of malignancy.

He concluded by stating that the combination of hypercalcemia and hypophosphatemia is found to be of diagnostic value in only 40% of cases. The tests that have been found reliable are demonstration of :—

(a) Reliable, reproducible hypercalcemia.

(b) Low or normal serum phosphate level.

(c) TRP below 90% on low phosphate diet and below 70% on high phosphate diet.

(d) Bone involvement shown by tracer study (Strontium infusion) or iliac crest biopsy.

(e) Increased serum alpha$_2$ and beta globulins without the electrophoretic changes of mycloma and sarcoidosis.

The Parathyroid Adenoma

E. H. Norris (1947) reviewed 322 cases from the literature. He found :—

(1) Multiple adenomas in 6.2% of cases.

(2) They were about equally frequent on right and left sides (Right 51.6% and Left 47.4%).

(3) The lower parathyroids were found to be involved about five times as frequently as the upper (42.7% Rt. lower, 41.1% Lt. lower. 9% Rt. upper and 7.1% Lt. upper).

(4) In 10.7% of cases the adenoma was in an aberrant position. Of these 63.3% were in the mediastinum (i.e. 6.8% of all cases), 30% between sulci of the thyroid gland, and in 6.7% behind the oesophagus.

B. Marden Black (1958) in a separate review reported that 80% were single adenomas with multiple adenomas in 10%; Primary or Wasserhelle hyperplasia in 10% and carcinoma in 1-2% of cases. His figures are closely similar to those of B. Castleman.

Castleman (1952) classified three groups of enlargements of the parathyroid gland viz :—

(1) **Primary Hyperparathyroidism**

(a) Adenomas which may be single or multiple.

(b) Primary hyperplasia and hypertrophy of all four glands.

(c) Carcinoma.

(2) **Secondary Hyperparathyroidism**
Hyperplasia of all four glands.

(3) **Non-functional Enlargements**
Oxyphil adenomas, cysts, carcinoma which may be primary or metastatic.

History and mode of presentation of hyperparathyroidism

Fuller Albright (1948) recently reviewed the "Austro-German Pathological Approach and the American Physiological Approach to the elucidation of Hyperparathyroidism". In 1880 Sandstrom discovered the "Glandulae Parthyreoideae" and in 1891 von Recklinghausen described Osteitis Fibrosa Cystica. It was Askanazy in 1903 who described a parathyroid tumour in a case of osteitis fibrosa cystica and in 1925 Mandll removed a parathyroid tumour on a similar type of case. In between there was Erdhein and Schlangenhaufer who correlated the glandulae parthyreoideae to calcium metabolism, ostcomalasia and osteitis fibrosa cystica.

In America in 1900 Jacques Loeb found the relationship of calcium in body fluid to contractility of muscle. Hanson (1924) and Collip (1925) independently extracted the active principle of parathyroid gland. It was Cope in 1925 who found high serum calcium levels in experimental hyperparathyroidism but in 1909 MacCallum and Voegtlin reported on low serum calcium levels in hyperparathyroidism. Isadore Greenwald in 1928 found that parathyroid extract puts dogs into negative calcium balance.

Unusual Presentation of Hyperparathyroidism

Hyperparathyroidism presenting with obvious metabolic bone disease is present in only about 25 per cent of cases.

B. Marden Black (1961) estimated that 5 per cent of all cases of radio-opaque urinary lithiasis and possibly 15% of cases of recurrent urinary lithiasis result from hyperparathyroidism.

Parathyroid hormone is a potent diuretic and in cases of polyuria and polydipsia this should be considered.

Oliver Cope et al (1957) reported on two cases with a review of five cases from past literature of Pancreatitis in cases of primary hyperparathyroidism. Pancreatitis may lower the elevated serum calcium levels of hyperparathyroidism.

Walter T. St. Goar (1957) reported on gastrointestinal symptoms as a clue to diagnosis of primary hyperparathyroidism. Symptoms may be related to the hypercalcemia, but cases have been reported as presenting with peptic ulceration and other dyspepsias.

Problems in the treatment of Hyperparathyroidism

Marden Black (1961) stressed three basic principles to be observed in the cervical exploration for a parathyroid adenoma viz :—

(1) Methodical identification of each of the parathyroid glands.

(2) Dissection must be bloodless to avoid obscuring the colour of the glands.

(3) Pathologist should be available to identify any lesions from fresh frozen sections.

Knowledge of the anatomy and recognition of the parathyroid glands is important. 90 per cent of superior glands lie rostral to the lower third of the thyroid lobes on a more dorsal plane. The inferior ones lie more lateral than the superior pair and in 95% of cases they are close to the inferior poles of the thyroid or within 3 cm. of the caudal extremities of the lobes.

The adenoma may lie within the sulci of the thyroid or in proximity to the cervical prolongation of the thymus or may be caught between contiguous structures.

The adenoma may be aberrant in position. Those larger than a gram may be displaced towards the mediastinum by negative intrathoracic pressure or gravity or swallowing movements. It may lie in the tracheo-oesophageal groove and come to lie in the posterior mediastinum with a vascular pedicle. Adenomas of the inferior gland may be displaced into the anterior or posterior mediastinum.

In the management of these parathyroid enlargements Marden Black (1961) divides them into five groups :—

(1) Two adenomas. Here it should be the routine practice to identify each of the four parathyroids before dealing with the adenomas.

(2) Primary or Wasserhelle-cell hyperplasia. Sufficient reliable hyperplastic tissue with intact blood supply should be preserved to prevent tetany.

(3) Multiple endocrine adenomas or Polyendocrine adenomas. Marden Black (1958) reviewed 14 cases with the rare combination of parathyroid tumours, islet-cell tumours of pancreas and tumours of the pituitary. Here either one normal gland or a viable fragment is retained if all parathyroids are involved.

(4) Adenomatosis of Parathyroids (Primary Chief-cell hyperplasia). In this condition all the parathyroid tissue is involved by hyperplasia of chief, or rarely, oxyphilous cells. Cope et al (1958) recommends a subtotal parathyroidectomy with preservation of portion of one gland.

(5) Parathyroid Carcinoma. This is a rare tumour. If diagnosed, a radical resection at initial surgical exploration should be carried out. However, the results are poor due to inadequate local excision or inoperability at diagnosis.

Mediastinal exploration is rarely required and has been reported in not more than 1 per cent of cases.

Following removal of a functioning adenoma the remaining hypoplastic glands may temporarily be unable to maintain a normal state of parathyroid function. To avoid this the patient is given pre-operatively calcium and phosphorus by means of milk and calciferol. Post-operatively, a careful watch is kept for signs and symptoms of hypocalcemia, and adequate replacement therapy given until the normal glands recover from the hypoplastic state.

Obvious parathyroid tumours in association with high serum calcium and metabolic bone diseases are diagnosed easily by most clinicians. It is the borderline cases with unusual presentations that are often missed. These constitute the larger percentage of parathyroid tumours. More and more cases are now detected by the urologists and in the future they will be often detected by the gastroenterologists.

SUMMARY

1. Four cases of hyperparathyroidism are reviewed only one of whom displayed the well-recognised picture of osteitis fibrosa cystica.

2. It is emphasised that hyperparathyroidism more often presents with symptoms and signs of renal calculus disease.

3. The clinical and chemical methods for recognizing hyperparathyroidism are reviewed, and the diagnostic criteria emphasised.

4. The literature has been reviewed from the historical aspect of parathyroid adenomas, action of parathyroid hormone, distribution and types of tumours and unusual manifestations.

5. Problems met with in the management of parathyroid tumours during neck exploration are discussed.

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