PRIMARY HYPERPARATHYROIDISM: THE CLINICAL AND BIOCHEMICAL ASPECTS IN 15 PATIENTS

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Since Mandl[1] established the causal relationship between a parathyroid adenoma and generalized osteitis fibrosa cystica, there has been steady progress in the study of hyperparathyroidism. Early cases were recognized by the presence of bone cysts, but the significance of renal calculi was soon established.[2, 3] Abnormalities in calcium and phosphorus metabolism were then associated with parathyroid hyperfunction. More recently, study of the direct effect of purified parathormone by Rasmussen has provided a definite physiological basis for these changes.[4]

The diagnosis of hyperparathyroidism has undoubtedly become more frequent during the past 5-10 years, and although it is possible that this trend reflects a true increase in the incidence of the disease, it is more likely that it can be accounted for by a wider acquaintance with the symptoms of the conditions, more careful screening of suspected cases and improvement in diagnostic procedures.[5, 6] Furthermore, as knowledge of the physiological actions of parathyroid hormone has accumulated, a wider variety of tests have been evolved in an attempt to measure minor deviations of parathyroid function from the accepted normal.

Primary hyperfunction of the parathyroid glands may result from a single adenoma, multiple adenomata, occasionally from diffuse hyperplasia, or rarely from a carcinoma. The aetiology of these changes, however, is still unknown. A low dietary calcium was suggested as a contributory factor, but Dent *et al.* were unable to confirm this.[8] Familial occurrence of this disease has been reported, usually owing to adenomata.[9, 10]

Patients with hyperparathyroidism secondary to chronic renal failure or steathorrhoea may develop autonomous parathyroid adenomata in rare instances.[11-13] The autonomy of the tumour has been conclusively shown in one case of secondary hyperplasia owing to chronic renal failure in which the kidney condition was corrected by renal transplantation. In spite of a reversion to normal renal function hyperparathyroidism persisted and was found to be due to an autonomous parathyroid adenoma. This was later excised with resultant cure of the hyperparathyroidism.[14]

During the past 4 years 15 patients with primary and one with secondary hyperparathyroidism have been studied at the Johannesburg Hospital. The case of secondary hyperparathyroidism followed on long-standing renal failure and necessitated subtotal parathyroidectomy. This case has been reported previously and will not be discussed in this communication.[13] Of the 15 cases of primary hyperparathyroidism, 13 were due to solitary adenomata, one to multiple adenomata, and one to primary hyperplasia.

This paper reviews our experience of the clinical and laboratory features of the entity and compares this with that of other workers.

The clinical features are set out in Table I. The wide range of organ systems involved can be appreciated. Table II summarizes the clinical aspects and details the laboratory findings in each of the 15 patients. These tables provide the basis for the subsequent discussion.

TABLE I. CLINICAL FEATURES IN 15 CASES

	No. of cases
1. *Renal*	
Calculi	11
Nephrocalcinosis	2
Urinary infection	7
Renal impairment:	
(*a*) Mild	5
(*b*) Moderate	3
(*c*) Severe	1
2. *Hypertension*	
(Possibly secondary to renal disease)	5
3. *Musculoskeletal*	
Bone cysts	2
Arthralgia	2
Periarticular calcification	1
4. *Gastro-intestinal*	
Peptic ulceration:	
Duodenal	4
Gastric	1
Dyspepsia (without ulceration)	3
Anorexia and weight loss	6
Constipation	6
Pancreatitis (with calculus)	1
Parotitis (with calculus)	1
5. *Psychological*	
(*a*) Depression	5
(*b*) Paranoid psychosis	1
(*c*) Mental confusion (in *a* and *b*)	3
6. *Miscellaneous*	
Otosclerosis (at young age)	1

CLINICAL FEATURES

The clinical abnormalities set out in Table I show a cross-section similar to that described in larger series on primary hyperparathyroidism.[5, 6, 15] The presentation varies markedly from patient to patient and there is no acceptable explanation for this. The symptoms are, however, largely due to the effects and long-term results of hypercalcaemia.

Renal involvement is most important, for if the disease is not recognized at an early stage, irreversible damage leading to chronic renal failure may occur. The high incidence of renal calculi (10 out of 15 patients) is noteworthy, as is the elevation of the blood urea to mean values of more than 50 mg./100 ml. in 5 cases. The stones, which consist of calcium phosphate or calcium oxalate, are thought to occur because the calcium phosphate solubility product is exceeded in the presence of hypercalcuria.[16] However, infection and changes in urinary pH may also play a role.[17] Urinary tract infection was present in one-

TABLE II. SUMMARY OF THE CLINICAL PRESENTATION AND THE RESULTS OF THE INVESTIGATIONS IN THE 15 PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age	31	42	37	67	73	54	38	42	60	38	49	64	53	50	31
Sex	M	M	F	M	M	F	F	F	M	M	F	F	F	F	F
Clinical features:															
Renal calculi	+	+	+	+	+	+	–	–	+	+	+	+	–	+	–
Skeletal and joint pain:															
Bone cysts (BC)	–	–	–	–	–	+(BC)	+(BC)	–	–	–	–	–	–	–	–
Joint pain (JP)	–	–	–	–	–	–	–	–	–	–	–	–	+(JP)	+(JP)	–
Dyspepsia (with or without ulceration)	–	+	–	+	+	+	–	+	–	+	–	–	+	+	–
Disturbance of psyche	+	–	+	+	+	–	–	–	–	–	–	–	+	+	–
Other	–	–	–	–	–	–	–	*	–	–	†	–	‡	§	¶
Blood pressure mm.Hg	140/105	125/90	130/90	120/75	140/85	130/100	150/100	120/80	185/115	130/60	140/90	140/90	180/100	108/60	110/70
Laboratory findings:															
Urinary protein	+	–	–	+	–	+	–	–	–	–	+	–	–	+	+
Increased cells with bacteriuria	–	–	–	+	–	+	–	–	–	–	+	–	–	+	+
														A**	B**
Serum calcium (mg./100 ml.)	11·0–13·5	11·5–13·5	11·2–12·0	9·4–10·0	10·6–15·4	12·0–14·0	13·8–15·2	10·4–11·2	10·6–13·2	10·6–11·6	10·0–16·0	11·6–12·0	11·6–14·8	11·2–14·4	11·4–14·4	12·2–15·6
Serum phosphorus (mg./100 ml.)	2·4–2·6	2·0–2·6	2·1–3·3	3·2–5·0	1·1–3·6	2·0–4·0	0·8–2·4	3·4–4·0	1·4–3·3	2·2–3·6	1·9–3·4	1·7–2·3	1·7–3·2	2·2–5·8	2·0–3·4	1·6–2·6
Alkaline phosphatase (KA units)	7·4	3·6	7·5	8·7	12·4	55·7	68·1	6·5	8·2	6·4	4·4	10·0	6·4	11·1–23·0	14·0–21·0	13·6–21·0
Blood urea (mg./100 ml.)	32	30	16	52–114	48–68	52–86	26	30	24–40	26	67–94	25	27–44	83–234	25	35
Urinary calcium (mg./24 hours)	650	440	302	138	108	198	–	–	402	583	140	–	283	350	343	500
Urinary phosphorus (mg./24 hours)	1,220	966	440	–	374	504	–	–	1,168	725	664	–	1,860	300	–	1,630
Creatinine clearance (ml./min.)	110	135	61	40–50	75	51	120	–	100	100	38	106	55–62	7·3–18·4	48–74	52–56
Phosphate clearance (ml./min.)	20·9	25·8	15·0	13·0–28·0	20·2	18·0	19·5	–	26·0–26·8	27·2	12·3–14·5	12·7	9·1–19·1	3·3–9·6	13·4–21·0	11·5–19·3
% TRP	81	81	76	64–70	73	65	84	–	74	73	62	88	68–83	48–73	58–78	66–78
FEI	+0·12	+0·13	+0·20	+0·13 to +0·37	+0·23 to +0·40	+0·30	+0·10	–	+0·20 to +0·30	+0·26	+0·29	+0·10	+0·10 to +0·26	+0·11 to +0·35	+0·16 to +0·38	+0·18 to +0·33
X-ray features: N = No abnormality; LD = Erosion of lamina dura; OFC = Osteitis fibrosa cystica; LAC = Ligamentous and arterial calcification; PC = Pancreatic calcification	N	N	N	N	LD	OFC	OFC	N	N	N	N	N	LD & LAC	N	LD & PC	
Nephrocalcinosis = (NC)	–	–	–	–	–	–	–	–	–	–	NC	–	–	NC	–	–
Histology (i) Adenoma – (Ad) Cell type: Chief = Ch, Clear = Cl; (ii) Primary hyperplasia = (PH)	Ad (Ch)	Ad (Ch)	Ad (Ch & Cl)	Ad (Ch)	Ad (Ch)	Ad (Ch)	Ad (Ch)	Ad (Cl)	Ad (–)	Ad (Ch)	Ad (Ch)	Ad (Ch)	Ad (Ch) & Cl)	PH	Ad (Ch & Cl)	Ad (Ch)

* The adenoma was palpable in the neck.
† Calculous parotitis occurred.
‡ The signs of Cushing's syndrome were present. Bilateral adrenal hyperplasia was the cause.
§ Otosclerosis developed at an early age.
¶ Recurrent pancreatitis was the presenting feature.
A** Before removal of 1st adenoma.
B** Before removal of 2nd adenoma.

third of the cases, and may have been a factor in the frequency of hypertension. Only 2 patients had unequivocal evidence of nephrocalcinosis (cases 11 and 14).

A history of dyspepsia may suggest the diagnosis of hyperparathyroidism whether peptic ulceration is present or not. This symptom occurred in 8 cases, and may be due to increased gastric acid secretion. In some cases ulcerogenic islet-cell adenomata (Zollinger-Ellison syndrome) have occurred in association with parathyroid adenomata, resulting in hyperchlorhydria and peptic ulceration.[18, 19] Acute pancreatitis is an unusual but dramatic complication of hyperparathyroidism,[20] and may be the presenting feature of the disease (case 15).[21] Its pathogenesis is believed to be related to the formation of pancreatic calculi,[22] or to a direct toxic action of excess parathormone on the pancreas.[23, 24] It is noteworthy that sialolithiasis may also occur and cause obstruction and infection in the salivary glands (case 11). Anorexia, nausea, vomiting and progressive weight loss are frequently noted and severe constipation is usual.

The low incidence of florid bone disease is consistent with many recently reported series.[25-27] This is possibly the result of earlier diagnosis since involvement of bone is a late feature.[28] Dent has postulated that the parathyroid gland may produce 2 hormones, only one of which causes osteitis fibrosa cystica while the other exerts its major effects on the kidney tubule.[11] It should also be appreciated that bone involvement may be present for a long period before radiological changes become apparent. The classical X-ray signs are osteitis fibrosa cystica (cases 6 and 7), skeletal demineralization, loss of the lamina dura of the teeth (cases 5, 13 and 15), pathological fractures, and subperiosteal resorption of the phalanges and lateral aspects of the clavicles (case 6). Solitary giant-cell tumours may occur in bone (especially in the jaw), in hyperparathyroidism as exemplified by case 7. Soft-tissue calcification of the joint capsules, periarticular tissue and arterial walls, occurred in case 13.

The effects of hyperparathyroidism on the psyche are of great importance. Confusional and depressive states have been described and referred to as 'parathyroid psychosis'.[29-31] Five of our patients were severely depressed (cases 1, 3, 5, 6 and 13) and 2 improved remarkably after surgery. Episodes of confusion occurred in cases 5 and 14.

The combination of several vague symptoms may be a pointer to the diagnosis. A constant awareness of the entity is a prerequisite to the making of the diagnosis.

ILLUSTRATIVE CASES

The following 4 case histories are presented in detail in order to illustrate certain features:

Case 5. Primary Hyperparathyroidism in an Elderly Subject with a Resultant Psychosis

A 73-year-old White man was admitted to hospital with a presumptive diagnosis of carcinoma of the stomach. He had symptoms of epigastric pain, nausea and vomiting, with anorexia and weight loss, for a period of 6 months. Chronic constipation was troublesome and more recently he had suffered from polydipsia and polyuria. Irritability and depression had been present for some years, and over the previous few months he had developed persecutory delusions and become confused. The past history included an episode of renal colic 5 years before admission.

Apart from evidence of considerable weight loss, the physical examination was normal. However, he was mentally disturbed, with episodes of confusion and paranoia. During these episodes he resisted the attentions of the doctors and nurses and demanded to leave the hospital. A barium meal revealed a duodenal ulcer and a maximal histamine test demonstrated hyperchlorhydria. Routine urinalysis was normal. The tests of calcium and phosphorus metabolism (Table II and Fig. 1) provided strong evidence of hyperparathyroidism.

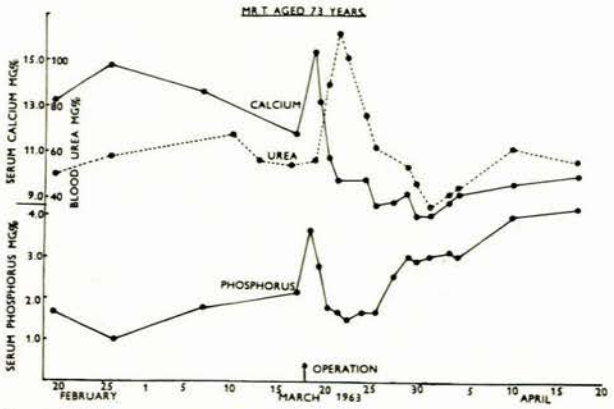

Fig. 1. This graph shows the return to normal of the serum calcium and phosphorus levels after the removal of a parathyroid adenoma. The blood urea levels were usually elevated and a further transient rise occurred postoperatively.

The parathyroid glands were explored and a benign chief-cell adenoma, ¾ inch in length, was removed from the right upper gland. The postoperative course was stormy. Hypocalcaemia lasting 5 days and a transitory rise in the blood urea occurred. Atrial fibrillation of ischaemic origin was controlled by digitalization. Bronchopneumonia occurred which responded to antibiotic therapy and duodenal haemorrhage necessitated blood transfusion. The paranoid ideas persisted for a few days, after which there was a dramatic improvement in his mental state. He became lucid and cooperative. The serum calcium and phosphorus levels returned to normal (Fig. 1) as did the tests of phosphate excretion. A report from his general practitioner 4 months later indicated that the patient had experienced remarkable mental and physical improvement.

Comment

This case illustrates the importance of being aware of the protean nature of the manifestations of parathyroid overactivity, some of which might easily be overlooked in the elderly. The mental changes and renal dysfunction may be more marked in elderly subjects.[32] A noteworthy feature was the improvement in his mental state after removal of the adenoma, which would indicate that advanced age is not a contraindication to operation.

Case 7. Primary Hyperparathyroidism in an African Subject with Bone Involvement

A 35-year-old African woman was referred to the Non-European Hospital in Johannesburg in 1962, because of a swelling on the right side of the jaw. She also complained of pain in the lower back and left hip over a period of 6 months. She had lost approximately 15 lb. in weight during the preceding year, and felt weak and tired. Two months before admission an operation had been performed on the jaw tumour, but total excision had proved impossible. Histology showed the typical features of an osteoclastoma, and the pathologist suggested the possibility of hyperparathyroidism.

On physical examination the blood pressure was 150/100 mm.Hg. A small mass with an overlying scar was present in the mandible. The lumbar spine was tender to percussion and the left hip was painful at the extremes of movement. Radiographs of the pelvis, lumbar spine and phalanges showed demineralization and numerous cystic areas.

The investigations carried out were strongly suggestive of hyperparathyroidism (Table II).

At operation a chief-cell adenoma of the left lower parathyroid gland was removed. The serum calcium rapidly fell,

reaching 7·6 mg./100 ml. on the 4th postoperative day. However, spontaneous tetany did not occur and the serum calcium level slowly rose to normal levels over the following week.

Comment

As far as we are aware, this is the first reported African patient with proven hyperparathyroidism. The clinical presentation is typical of hyperparathyroid involvement of the skeletal system. Whether the rarity of this condition in the African is due to dietary factors is unknown. Failure to present for investigation of the lesser symptoms is probable, but the pain in cystic bone disease or the symptoms of renal failure would certainly induce medical consultation. The calcium content of the African diet is low, and thus it is interesting to speculate that if the theory of Albright and Reifenstein[7] regarding the protective action of a high calcium intake on demineralization is correct, bony involvement would be expected in Africans with hyperparathyroidism, as in this patient.

Case 13. A Patient with Cushing's Syndrome and Primary Hyperparathyroidism

A 55-year-old White woman presented with severe depression which had increased steadily for 5 years. She had undergone extensive psychotherapy both as an outpatient and as an inpatient. There was no improvement and she was regarded as a case of psychoneurosis, with depression and emotional immaturity.

Other symptoms were backache, aching of the large joints, polyuria, and polydipsia. Constipation had been a problem for many years. She had been aware of facial hirsutes and increasing obesity of the trunk for 12 years.

She suffered from a peptic ulcer when 19 years old and intermittent dyspepsia had occurred since that time. Fibroadenosis of the left breast was proved by biopsy and because of active epitheliosis radiotherapy was given 5 years ago. A myomectomy was performed when she was 35 years of age and she experienced a normal menopause 7 years later.

On examination she was found to be very depressed and irritable with emotional lability. Adrenocortical hyperfunction was suggested by the following features: hirsutism of the face, arms and legs, and a receding hairline; central obesity with a buffalo hump, a degree of facial fullness and ruddiness, and a blood pressure of 180/100 mm.Hg. The genitalia were normal, but the pubic hair tended to be of masculine distribution. No history suggestive of endocrine disorder in other members of the family was obtained.

Investigations. The serum calcium level was repeatedly elevated and the tests shown in Table III provided confirmatory evidence of hyperparathyroidism. The radiological changes, namely erosion of the lamina dura, metastatic calcification of the ligaments of the hip joints and interphalangeal joints, and calcification of the peripheral arteries, were compatible with this diagnosis.

The full blood count was normal apart from a marked decrease in eosinophils. The estimation of serum sodium, potassium, chloride and bicarbonate yielded normal results.

The glucose-tolerance curve was normal when performed in 1960. In 1963 a diabetic curve resulted. The fasting blood-glucose level was 75 mg./100 ml. and after 50 G of glucose orally the results in mg./100 ml. were as follows: After ½-hour 126, after 1 hour 145, after 2 hours 140, after 3 hours 105, and after 3½ hours 65.

The response of the blood-glucose levels to insulin showed decreased insulin sensitivity, as expected in hyperadrenocorticism.

The plasma 17-hydroxycorticoids were elevated to 44 μg./100 ml. (normal range 7 - 20).

The studies of steroid excretion in the urine are recorded in Table III. The metapirone test was performed twice, administering 250 mg. 2-hourly for 24 hours and then collecting the urine over the next 24-hour period. Forty units of ACTH were used intravenously for the stimulation test.

X-rays of the pituitary fossa were normal. Intravenous pyelography with tomography showed no abnormality, but presacral air insufflation demonstrated mild bilateral enlargement of the adrenal glands.

TABLE III. THE RESULTS OF URINARY STEROID EXCRETION TESTS WHICH REFLECT HYPERADRENOCORTICISM IN CASE 13

	17-*Hydroxy-corticoids mg./24 hour urine*	17-*Keto-steroids mg./24 hour urine*
Normal range for female aged 55 ..	3–13	2–10
Basal values	12·4–21·8 mean 16·8	8·8–21·6 mean 16·1
ACTH stimulation test	32·0	23·0
Post metapirone (250 mg. 2-hourly)		
Test 1	26·0	19·9
Test 2	26·6	16·6
Dexamethasone suppression test		
Day 1—0·5 mg./6-hourly ..	19·7	14·1
Day 2—0·5 mg./6-hourly ..	12·9	14·9
Day 3—2·0 mg./6-hourly ..	9·9	11·5
Day 4—2·0 mg./6-hourly ..	9·1	11·3

The above tests showed hyperfunction of the adrenal cortex: the glands were mildly responsive to stimulation by ACTH and metapirone. Suppression by dexamethasone was incomplete. These results suggested either hyperplasia or a partially autonomous adenoma, while the presacral air-insufflation test was in favour of the former with bilateral involvement.

Other investigations done were: serum protein-bound iodine 3·5 μg./100 ml., serum cholesterol 244 mg./100 ml., urinary FSH in 24 hours over 48 mu. Total gastric acid in 1 hour after histamine stimulation 21 mEq. The blood-glucose curve after tolbutamide administration was normal.

Diagnosis. Primary hyperparathyroidism and bilateral adrenocortical hyperplasia were suggested by the clinical features and the above investigations.

Management. Exploration of the neck was carried out and a parathyroid adenoma situated in the left lower parathyroid gland was removed. Histological examination showed 2 discrete areas in the adenoma, one with predominantly chief cells and the other with mainly clear cells.

Subtotal bilateral adrenalectomy was subsequently undertaken. The glands were enlarged, and the excised adrenal tissue weighed 20 G. The hyperplasia, largely of the zona reticularis, was confirmed histologically.

Maintenance corticosteroid therapy has been necessary since the adrenalectomy.

The serum calcium and phosphate excretion tests have remained normal since the parathyroidectomy and the clinical signs of Cushing's syndrome have almost entirely disappeared. Despite the correction of both endocrinopathies, considerable depression has persisted, although the irritability and emotional lability have improved.

Comment

This patient suffered from 2 endocrine disturbances: primary hyperparathyroidism owing to an adenoma and Cushing's syndrome owing to adrenal hyperplasia. The possibility of an undetected basophil adenoma of the pituitary gland causing the adrenal hyperfunction exists. She falls into the category of a pluriglandular syndrome, also known as endocrine adenomatosis, or the syndrome of multiple endocrine adenomata (MEA). Abnormalities in more than one endocrine gland are found to be due to adenomata, or to hyperplasia in some instances.[40, 41] The adenomata may occur in 2 or more of the following glands: the parathyroids, the pituitary (either basophil or eosinophil adenomata), the pancreas, the thyroid, or the adrenal cortex.[40, 41, 43] The pancreatic lesions may be ulcerogenic islet-cell adenomata causing the Zollinger-Ellison syndrome or less often insulin-secreting islet-cell adenomata resulting in hyperinsulinism. Adrenal hyperplasia may be associated, particularly when a basophil adenoma of the pituitary is present. The mechanism of causation of the syndrome is unknown, but it is often familial with an autosomal dominant inheritance and variable expressivity.[41-43]

Thirty-five percent of cases of MEA have peptic ulceration usually of the duodenum or upper jejunum associated with hyperplasia of the gastric mucosa and excessive gastric acid secretion.[42-44]

At least 10 other cases of coexisting hyperparathyroidism and Cushing's syndrome have been reported.[5, 6, 43, 45] The association, though unexplained, occurs with a frequency which precludes mere coincidence.

The serum calcium levels are usually normal in Cushing's syndrome.[46] When elevated levels are found, associated hyperparathyroidism is a possible explanation and further investigations should be performed.

Case 14. A Patient with Severe Renal Dysfunction Secondary to Primary Hyperplasia of the Parathyroid Glands

A 52-year-old White woman presented with memory impairment, confusion, unsteadiness and postural hypotension of 4 months' duration. Further symptoms were anorexia, weight loss and pain in the ankles and wrists. Polydipsia and polyuria with nocturia had been present for some months, and during this period she had been treated for moderate hypertension.

On examination the blood pressure was 140/90 mm.Hg and calcification was noted in the pterygia of the eyes. Apart from mild confusion and memory loss, there were no other abnormal neurological signs.

The haemoglobin was 10 G/100 ml. and the blood urea 235 mg./100 ml. The serum potassium was 3·0 mEq./l., plasma bicarbonate 30·0 mEq./l., but the serum sodium and chloride levels were normal. The serum proteins were 7·2 G/100 ml., the albumin being 3·0 G/100 ml., and the globulin 4·2 G/100 ml. The urine showed a trace of protein, but the white and red cell excretion rates were within normal limits and cultures were sterile. The specific gravity range of the urinary concentration — dilution test was from 1·014 to 1·004, and the creatinine clearance was considerably impaired (10 ml./min.). Despite the high blood urea level, the serum calcium level was elevated to 13·2 mg./100 ml. (Table II).

Urinary phosphate excretion tests were unreliable because of severe renal impairment. After the administration of intravenous calcium (40 mg. per kg. body weight over 4 hours), there was no rebound increase in urinary phosphate excretion over the following 24 hours.[33] This finding indicated a failure to suppress parathyroid gland function and this favoured the diagnosis of hyperparathyroidism. The cortisone suppression test[34] failed to lower the serum calcium level. This result suggested that the hypercalcaemia was probably not a result of sarcoidosis, vitamin-D intoxication, myelomatosis, carcinomatous metastases or the milk-alkali syndrome. A radiological skeletal survey was normal and nephrotomograms did not reveal nephrocalcinosis or calculi. The electrocardiogram showed evidence of hypokalaemia.

It was not clear whether this was a case of primary hyperparathyroidism resulting in renal failure, or whether the parathyroid activity was secondary to prolonged renal disease.

Therapy consisted of correction of the unexplained hypokalaemia and conservative management of the renal failure. When the patient's condition had improved, parathyroidectomy was performed. The upper parathyroid glands were enlarged to twice their normal size while the lower glands appeared normal. No adenoma was found in the neck or upper mediastinum. Both upper and the right lower glands were removed, leaving the smaller left lower gland *in situ*. On histological examination there was hyperplasia of 'water clear' cells and an increase in fat. Postoperatively the serum calcium fell to normal levels and the blood urea stabilized at approximately 140 mg./100 ml. The serum calcium has subsequently remained normal.

One year after the operation the patient experienced left renal angle colic and a retrograde pyelogram demonstrated a calculus partially obstructing the lower ureter. At operation a non-functioning hydronephrotic left kidney with nephrocalcinosis was found and a nephrectomy was performed. On direct palpation, the right kidney was found to be involved to a moderate extent by nephrocalcinosis. The postoperative course was uneventful and renal function has remained static with blood urea levels of approximately 100 mg./100 ml. over an 8-month period.

Comment

It has usually not been possible to correlate the clinical presentation of hyperparathyroidism with the histology of the parathyroid glands,[35, 36] but Castleman and Cope[37] have pointed out that all their cases of primary hyperplasia were associated with renal involvement and only 2 had skeletal changes, which were minimal in extent. Hellstrom and Ivemark[5] contrasted the findings in 121 patients with adenomata and 17 with primary hyperplasia of the parathyroid glands. The most notable difference was a greater frequency of severe renal damage, significant hypertension, and markedly raised serum calcium values in primary hyperplasia. This patient is thus an example of parathyroid hyperplasia presenting with nephrocalcinosis, calculi and advanced renal failure in the absence of other signs or symptoms attributable to hyperparathyroidism. The problem of differentiating primary hyperparathyroidism with renal failure from secondary hyperparathyroidism following long-standing intrinsic renal disease arose. That this may be a very real difficulty is illustrated in a number of cases described by Dent,[11] but the absence of bone involvement in our patient made the diagnosis of secondary hyperparathyroidism unlikely.[38] The predominant enlargement of the upper glands and the clear cell hyperplasia is in keeping with other reports of primary hyperplasia of the parathyroid glands.[39]

Case 15. A Patient Presenting with Recurrent Pancreatitis

This case has been previously reported by Green[21] and only brief comment is called for. She was a young woman aged 31 who presented with recurrent acute pancreatitis during pregnancy with radiological pancreatic calcification. Primary hyperparathyroidism was diagnosed on the basis of investigations as in Table II. Two neck explorations were necessary since the biochemical abnormalities persisted after the removal of one adenoma. A second adenoma was located and excised, and thereafter the biochemical tests returned to normal.

BIOCHEMICAL FINDINGS

Although a presumptive diagnosis of hyperparathyroidism may be entertained on the basis of the history, examination and radiological findings, laboratory tests will always be necessary to establish the presence of the disease with certainty. This is particularly relevant to patients presenting exclusively with renal calculi, in whom the diagnosis is entirely dependent on biochemical measurements.[25] Primary hyperparathyroidism classically causes a combination of characteristic biochemical disturbances, viz. hypercalcaemia, hypophosphataemia, hypercalciuria, hyperphosphaturia and a raised plasma alkaline phosphatase. The specificity and sensitivity of laboratory tests have improved with the introduction of modifications, particularly those pertaining to the renal handling of phosphate, and the measurement of the ionizable fraction of the serum calcium.

Hypercalcaemia

The fasting serum calcium level is the most emphasized single investigation, and while a raised level is an important diagnostic point, there are a number of difficulties which should not be overlooked. The patient should be in the fasting state and blood collected without venous occlusion, since this tends to elevate the serum calcium level.[11] The estimation of calcium is difficult and in a routine laboratory dealing with many samples daily, inaccurate results may occur.[5] Moreover, while hyperparathyroidism is an important cause of hypercalcaemia, sarcoidosis, hypervitaminosis D, disseminated malignancy, the milk-alkali syndrome and hyperthyroidism and other rare causes must be carefully excluded before a definitive diagnosis can be made. Of the 15 cases listed in Table II, 14 had raised serum calcium levels at some time during their pre-operative period of investigation. Even when

every precaution is taken to minimize technical errors, the serum calcium does vary slightly over a period of time.[47] Minimally raised values may therefore be difficult to interpret and need repeating. This fluctuation has also been observed in normals and there is a trend towards higher levels in older age groups.[48] Furthermore, the occurrence of hyperparathyroidism with repeatedly normal serum calcium values has been described,[49-51] and one of our patients falls into this category. A normal or borderline serum calcium level is particularly liable to occur in the presence of renal failure or with low serum albumin levels. Lloyd and Rose[52] have suggested that a rise in the ionizable fraction of serum calcium is the most sensitive, and at times, the only detectable abnormality in hyperparathyroidism. However, the methods available for its determination are difficult and time-consuming. The estimation of the diffusible fraction of the serum calcium has proved unreliable.[5]

Hypercalciuria

To be of value, the 24-hour urinary excretion of calcium must be measured after the patient has been on a low calcium diet for a number of days.[53] Hypercalciuria is present in many conditions including vitamin-D intoxication, sarcoidosis and idiopathic hypercalciuria. Recently Kleeman *et al.*[54] have shown that parathormone may actually decrease the renal clearance of calcium and this may explain the normal values that are sometimes found in hyperparathyroidism. In the presence of renal failure, calcium excretion is usually low.

Alkaline Phosphatase

A raised serum alkaline phosphatase is indicative of bone involvement, and may be present before the appearance of radiological signs (case 14).[55]

Tests of Phosphorus Handling

In the opinion of many, urinary phosphorus excretion tests are of great value in the diagnosis of hyperparathyroidism. Since it has been demonstrated that parathormone has both hypercalcaemic and hyperphosphaturic actions,[56] it would seem reasonable to measure both the known effects of the hormone. In regard to the test which should be used, many divergent opinions have been expressed.

(a) *Hyperphosphataemia*

Measurement of the serum inorganic phosphate is only of limited value,[57] because many patients with hyperparathyroidism have normal levels (Table I). Hypophosphataemia may, however, also occur in association with a number of intrinsic disorders of the renal tubule.[53, 58] In renal failure a rise in the serum phosphate occurs and this may mask the effect of hyperparathyroidism. As glucose or insulin administration lowers the serum phosphate, the serum phosphate should be measured while the subject is in the fasting state. Age, too, should be taken into consideration, for the serum inorganic phosphate falls with advancing years.[47] It is important to note that alkalosis, either metabolic or respiratory, is a common cause of hypophosphataemia. This may occur in anxious subjects who hyperventilate.[59]

(b) *Hyperphosphaturia*

In the renal handling of phosphate, patients with hyperparathyroidism differ markedly from normal subjects. All tests of urinary phosphate excretion are based upon the excessive renal loss of phosphate which occurs in hyperparathyroidism, and since the serum level is usually low, any ratio of urinary to serum phosphate should be increased. Although the various tests are based on the same principle, a number of modifications have been introduced in order to improve their diagnostic value. Those in common use are the phosphate clearance (Cp); the percentage of filtered phosphate reabsorbed by the renal tubules (%TRP); the phosphate excretion index (PEI); the maximal tubular reabsorption rate of phosphate (Tm.P) and the amount of phosphate reabsorbed per 100 ml. of glomerular filtrate. None of these has been widely accepted, and many conflicting reports claiming superiority of one method over the remainder have appeared. It is in fact surprising that such divergent results should be obtained with comparatively simple determination.

The phosphate clearance is favoured by Kyle and his co-workers,[57, 60] but we have found that errors in urine collection are difficult to avoid if a catheter is not used and that the test is therefore often unreliable. Similar problems have been encountered by others.[61, 62] The %TRP is derived from the ratio of Cp to glomerular filtration rate (GFR) and obviates the problem of incomplete bladder emptying. However, this measurement fluctuates with changes in the serum phosphate[63] and the filtered load,[62] and although widely used,[64, 65] has proved disappointing.[62, 66]

The PEI was devised to correct the $\frac{Cp}{GFR}$ for the effect of different serum phosphate levels.[66] It is accepted by some as the most reliable of this group of tests,[25, 61] but this is disputed by others.[33, 60] The amount of phosphate reabsorbed per 100 ml. of glomerular filtrate is calculated by multiplying the serum phosphate by the $\frac{Cp}{GFR}$,[60] but does not seem to have any advantage over the other tests.[61, 68] The results of these investigations in 13 patients with parathyroid adenomata are shown in Fig. 2. Of this group of tests, the PEI was the most reliable indication of hyperparathyroidism and was abnormal at some stage in every case. Furthermore, this test reverted to normal after excision of the adenoma in every case with the exception of one case where the renal insufficiency was marked.

The PEI was persistently raised in the patient with repeatedly normal serum calcium levels (case 4). The patient with 2 parathyroid adenomata (case 15) had a normal PEI during pregnancy, even though the serum calcium level was raised. Other cases of primary hyperparathyroidism have been diagnosed during pregnancy,[69, 70] but we were unable to find values for phosphate excretion tests during normal pregnancy. Therefore, the Cp, %TRP and PEI were measured in 20 pregnant women. All results fell within the normal range, thus making it unlikely that the discrepant finding was due to this factor. The usefulness of the PEI is compared with the levels of serum calcium and phosphate in the diagnosis of hyperparathyroidism in Fig. 3.

Phosphate excretion tests are altered in many conditions, and abnormal findings are not confined to hyperpara-

thyroidism. For instance, osteomalacia, congenital renal tubular defects, sarcoidosis, uraemia, Cushing's syndrome, hyperthyroidism, cirrhosis, multiple myeloma, hypokalaemic nephropathy, hyperglycaemia and a high phos-

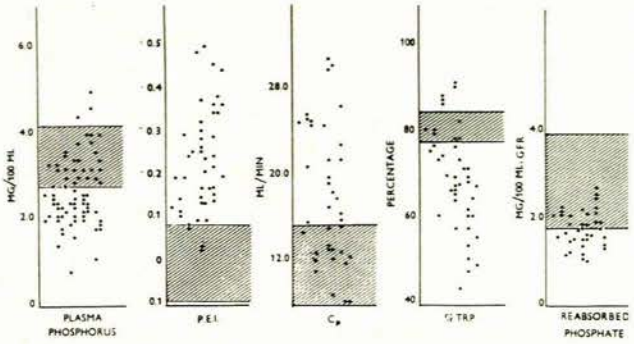

Fig. 2. The relative diagnostic value in primary hyperparathyroidism of the plasma phosphorus level, the phosphate excretion index (PEI), the phosphate clearance (Cp), the percentage tubular reabsorption of phosphate (% TRP), and the reabsorbed phosphate (expressed as mg./100 ml. GFR) in this series of patients are compared. The shaded areas represent the normal range for each test. The phosphate excretion index is seen to be superior to the other phosphate excretion tests, and the plasma phosphorus is least reliable.

phorus diet, as well as hyperparathyroidism may depress the %TRP.[60] The PEI is similarly abnormal in many of these conditions.[67] Moreover, McGeown[53] has obtained results in the hyperparathyroid range in a group of patients having renal calculi, hypercalciuria, and a low serum phosphate, but no detectable parathyroid abnormality at operation. Phosphate deprivation has been used to intensify the hypercalcaemia in doubtful cases of hyperparathyroidism, but the resultant changes in phosphate excretion tests have not been of great help in diagnosis,[62] although reduction in the tubular reabsorption of phosphate has been observed.[60]

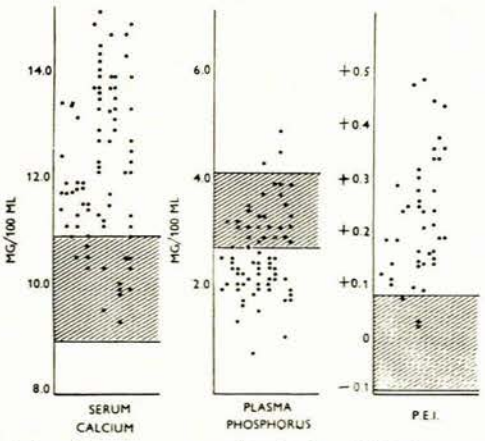

Fig. 3. The phosphate excretion index (PEI) is compared with the levels of serum calcium and plasma phosphorus in primary hyperparathyroidism. The shaded area represents the normal range for each test. The PEI is shown to be the most reliable diagnostic aid. The serum calcium levels were sometimes in the normal range and almost one-third of the plasma phosphorus levels were normal.

(c) *Diurnal Rhythm*

Normal subjects show a diurnal variation in urinary phosphate excretion, with low values in the early morning (4 - 8 a.m.) and gradual increase in the afternoon until a peak is reached between 8 and 12 p.m.[71, 72] Yendt and Jaworski[62] noted the disappearance of the rhythm in 3 patients with hyperparathyroidism and suggested that this may be of diagnostic value. We have followed the rhythm in normal subjects, in 4 patients with hyperparathyroidism and in 2 with hypoparathyroidism. The test was performed in the fasting state, the urine being collected at 2-hourly intervals and the results expressed as the ratio of urine phosphate to creatinine. The diurnal variation was absent in the patients with hyperparathyroidism but present in the normal subjects and in the patients with hypoparathyroidism. If these observations are confirmed in a larger series, the test may be of diagnostic significance.

Miscellaneous Tests

Many other tests have been described as an aid to the diagnosis of hyperparathyroidism. However, as our experience with each one is limited to a small number of patients, they will not be discussed in detail. The administration of cortisone causes a fall in the serum calcium level to normal in patients who have hypercalcaemia owing to sarcoidosis, multiple myeloma, milk-alkali syndrome, hypervitaminosis D, metastatic carcinoma, or idiopathic hypercalcaemia of infancy, while the serum calcium level in cases of hyperparathyroidism is usually unaffected.[11] Calcium infusion tests have been extensively used, but as yet there is no agreement on the best serum and urinary measurements or their interpretation. In this regard Howard *et al.*,[71] and Pronove and Bartter[33] have advocated the estimation of the 24-hour urinary phosphate; Kyle *et al.*[72] measured the phosphate excretion 8 - 10 hours after the infusion when parathyroid suppression is maximal; Nordin[61] stressed that 4-hourly urine collections over 24 hours are important, while Goldsmith and Forland[73] have noted the effect of a rapid calcium infusion on the diurnal excretory rhythm of urinary phosphate. A similar infusion has been used with estimation of the 4-hour retention of calcium, since this is low in the presence of parathyroid over-activity.[74] Recently a low-phosphate, low-calcium diet, which accentuates the hypercalciuria of hyperparathyroidism, has been described.[74] Bone biopsy may also be helpful, but the findings in early osteitis fibrosa are not specific.[6] The availability of a short-lived radioactive isotope of calcium, ^{47}Ca, with a half-life of 4 - 7 days, has given added impetus to the study of calcium dynamics in bone disorders. The pattern of disappearance of an injected dose of isotope may be applied to the diagnosis of hyperparathyroidism in the future.[75]

The Tests in the Doubtful Case

The major problem in hyperparathyroidism centres about its diagnosis in patients with minimally deranged diagnostic tests. When it is the serum calcium level that is marginally raised, there is general agreement that a diagnosis of hyperparathyroidism is justified, providing that other causes of this abnormality are excluded. However, when some other test is abnormal in the presence of normocalcaemia, the position is less clear. Howard believes that these patients should not be operated upon, for it is possibly hypercalcaemia alone that is responsible for renal damage in this condition.[15] This assumption is probably unjustified, for many cases of proved hyperparathyroidism with repeatedly normal serum calcium levels, but with renal involvement especially in the form of calculi, have been described. This combination occurred in case 4, who, despite a normal serum calcium level, presented with peptic ulceration and renal calculi. There was considerable

clinical improvement postoperatively, and the blood urea showed moderate improvement. Moreover, with the discovery of calcitonin, a calcium-lowering hormone, the unusual finding of normo- or even hypocalcaemia in a patient with a parathyroid tumour can be theoretically explained.

If this contention is tenable, then investigations must be chosen to give a reliable indication of the presence of parathyroid over-activity, when the serum calcium level is not diagnostic. There is no widespread agreement on the choice of tests, with the result that different criteria are used as an indication for operation in various centres. Nordin stresses the value of the PEI and presumably used it as the basis for operating on 3 patients with normocalcaemia in his series.[61] A further patient with a normal serum calcium and raised PEI underwent a negative exploration. Pronove and Bartter, on the other hand, only operated on suspected cases of hyperparathyroidism when both the calcium infusion and the phosphate and calcium-deprivation tests were abnormal.[33] Nine of 20 such patients had normal serum calcium levels and some had normal phosphate excretion indices. The pathological description of the presence of 'foci of parathyroid hyperplasia' in a number of the removed glands, has raised doubts as to the exact nature of the condition with which they were dealing. Yet another group of patients, many with normocalcaemia, underwent surgery for hyperparathyroidism if they failed to show an alteration in their phosphaturic rhythm following a rapid calcium infusion.

It appears that clinically significant hyperparathyroidism does exist in the absence of hypercalcaemia, but that no other test can be consistently relied upon to indicate its presence. This dilemma may be solved when parathormone assays become readily available. However, until that time, it would seem reasonable to base the decision to explore the neck on a careful clinical assessment, together with a combination of the investigations discussed above. Thus, the most important tests in investigating a case of suspected hyperparathyroidism are the following:

1. The fasting serum calcium level which should be done on a sample collected without venous compression,[11] and repeated several times.

2. If there is hypercalcaemia or even if the serum calcium is normal with symptomatology strongly suggestive of hyperparathyroidism, a phosphate excretion index (and the other tests of renal phosphate loss) should be performed.

3. If doubt remains, the additional tests discussed above may prove necessary. If a reliable estimation of serum ionized calcium is possible, this is of value, and the effect of corticosteroid administration on the serum calcium levels will help rule out other causes of hypercalcaemia.

TREATMENT

The surgical removal of the hyperfunctional parathyroid tissue is the only curative procedure. Adequate exploration of the neck and upper mediastinum from above, is done as a routine in search of one or more parathyroid adenomata either in a normal or aberrant situation. Frozen sections done in theatre are of great help to the surgeon. If no adenoma or hyperplastic parathyroid tissue is found, exploration of the anterior and posterior mediastinum is indicated provided the criteria for diagnosis are adequate.[76] The usual sites for aberrant parathyroid glands are the neck or the mediastinum, either anteriorly or occasionally posteriorly. Dent has stated that a temporary drop in the serum calcium level after an unsuccessful search for a parathyroid tumour in the neck implies damage to the tumour, undiscovered at surgery. A further search in the same area must then be undertaken. If no change occurs in the serum calcium levels after the unsuccessful search in the neck, the mediastinum should be explored.

In the case of hyperplasia, subtotal parathyroidectomy is done, with removal of three glands and possibly part of the fourth gland. In secondary hyperplasia Stanbury *et al.*[77] recommend leaving 200 mg. of functional parathyroid tissue, but Dent has suggested total parathyroidectomy.

Surgery is indicated even in the face of significant renal impairment since it is vital that further damage to the kidney by hypercalcaemia be prevented. Although the operation requires a painstaking search, it is not a shocking procedure, and even elderly patients should have surgery when hyperparathyroidism is diagnosed.

The infrequency of negative explorations in suspected hyperparathyroidism suggests either that the criteria for diagnosis are very reliable or that the indications for exploration of the neck are too rigid. When the symptoms are suggestive and the laboratory investigations doubtful, exploration of the neck would seem a reasonable undertaking in view of the serious renal complications of hyperparathyroidism.

SUMMARY

1. The clinical and laboratory findings in 15 cases of primary hyperparathyroidism are presented.

2. The manifestations of primary hyperparathyroidism are protean. Renal calculi were the commonest feature in this series, but the frequency of dyspepsia with or without peptic ulceration, and of disturbances in the psyche, are worthy of emphasis.

3. Bone cysts occur late in the disease and are now relatively uncommon. Radiological changes were present in one-third of the cases of hyperparathyroidism.

4. The 4 cases reported in detail demonstrated the following features:

(*i*) The presence of a 'parathyroid psychosis' and the benefits of surgery in an elderly subject.

(*ii*) The severe renal impairment that can result in primary hyperplasia of the parathyroid glands.

(*iii*) The occurrence of osteitis fibrosa cystica in an African woman, probably the first case of hyperparathyroidism reported in this racial group.

(*iv*) The association of primary hyperparathyroidism and Cushing's syndrome with comments on the entity of endocrine adenomatosis.

5. The range of helpful investigations and the local experience in their use is discussed. The serum calcium levels and the studies on renal excretion of phosphate such as the phosphate excretion index, provided the most useful diagnostic aids.

6. A constant awareness of the condition is essential in order that the diagnosis may be made early and the severe renal complications prevented by early surgical intervention.

We wish to thank Prof. J. H. Gear, Dr. B. Goldberg, Dr. T. H. Bothwell and other colleagues whose patients are included in this series; Mr. J. A. Myburgh who performed the surgery in some of the patients; and Prof. G. A. Elliott, for guidance and helpful criticism. We are grateful to Prof. H. B. Stein and Dr. G. S. Getz for advice and for providing facilities for the biochemical investigations. We are also grateful to the Photographic Unit of the Department of Medicine for the photographs.

REFERENCES

1. Mandl, F. (1926): Zbl. Chir., **53**, 260.
2. Albright, F., Baird, P. C., Cope, O. and Bloomberg, E. (1934): Amer. J. Med. Sci., **187**, 49.
3. Albright, F., Aub, J. C. and Baver, W. (1934): J. Amer. Med. Assoc., **102**, 1276.
4. Rasmussen, H. (1961): Amer. J. Med., **30**, 112.
5. Hellstrom, J. and Ivemark, B. I. (1962): Acta med. scand., suppl. 294, 8.
6. Gordan, G., Eisenberg, E., Roken, H. F., Gardner, B. and Hayashida, G. T. (1962): Recent Progr. Hormone Res., **18**, 297.
7. Albright, F. and Reifenstein, E. C. jnr. (1948): *The Parathyroid Glands and Metabolic Bone Disease.* Baltimore, Maryland: Williams and Wilkins.
8. Dent, C. E., Hartland, B. V., Hicks, J. and Sykes, E. D. (1961): Lancet, **2**, 336.
9. Frohner, R. N. and Wolgamot, J. C. (1954): Ann. Intern. Med., **40**, 765.
10. Jackson, C. E. (1958): *Ibid.*, **49**, 829.
11. Dent, C. E. (1962): Brit. Med. J., **2**, 1495.
12. Case Records of Massachusetts General Hospital (1963): New Engl. J. Med., **268**, 943.
13. Stables, D. P., Levin, N. W., Rubenstein, A. H., Berk, M. E. and Abrahams, C. (1964): Ann. Intern. Med., **61**, 531.
14. McPhaul, J. J. jnr., McIntosh, D. A., Hammond, W. S. and Park, O. K. (1964): New Engl. J. Med., **271**, 1342.
15. Howard, J. E. (1962): Trans. Coll. Phycns. Philad., **32**, 55.
16. Rasmussen, H. and Reifenstein, E. C. jnr. *in* Williams, R. H., ed. (1962): *Textbook of Endocrinology*, p. 731. Philadelphia: Saunders.
17. Nordin, B. E. C. (1958): J. Endocr., **18**, 25.
18. Zollinger, R. M. and Craig, T. V. (1960): Amer. J. Med., **29**, 761.
19. Mieher, W. C., Hartsock, R. J., Geohas, M. C., Ballard, H. S. and Frame, B. (1962): J. Amer. Med. Assoc., **179**, 854.
20. Turchi, J. J., Flandreau, R. H., Forte, A. L., French, G. N. and Ludwig, G. D. (1962): *Ibid.*, **180**, 799.
21. Green, H. (1963): South African Journal of Surgery, **1**, 61.
22. Cope, O., Culver, P. J., Mixter, C. G. jnr. and Nardi, G. (1957): Ann. Surg., **145**, 857.
23. Heuper, W. (1927): Arch. Path., **3**, 14.
24. Hoar, C. S. and Gorlin, R. (1958): New Engl. J. Med., **258**, 1052.
25. Harrison, A. R. (1963): *The Scientific Basis of Medicine Annual Reviews*, p. 266. London: The Athlone Press.
26. Black, B. M. (1961): Surg. Clin. N. Amer., **41**, 1061.
27. Cope, O. (1960): Amer. J. Surg., **19**, 394.
28. Aurbach, G. D. and Potts, J. T. jnr. (1964): *Advances in Metabolic Disorders*, vol. 1, p. 45. New York: Academic Press.
29. Eitinger, L. (1942): Nord. Med., **14**, 1581.
30. Fitz, T. E. and Hallman, B. L. (1952): Arch. Intern. Med., **89**, 547.
31. Bogdanoff, M., Woods, A. H., White, J. E., Engel, F. L. (1956): Amer. J. Med., **21**, 583.
32. Gershberg, H., Jones, S., Stiff, D. P. (1962): J. Amer. Med. Assoc., **182**, 136.
33. Pronove, P. and Bartter, F. C. (1961): Metabolism, **10**, 349.
34. Dent, C. E. (1956): Brit. Med. J., **1**, 230.
35. Castleman, B. and Mallory, T. B. (1935): Amer. J. Path., **11**, 1.
36. Woolner, L. B., Keating, F. R. jnr. and Black, M. B. (1952): Cancer (Philad.), **5**, 1069.
37. Castleman, B. and Cope, O. (1951): Bull. Hosp. Jt. Dis., **12**, 368.
38. Gilmour, J. R. (1947): *The Parathyroid Glands and Skeleton in Renal Disease.* London: Oxford University Press.
39. Castleman, B. (1952): *Tumours of the Parathyroid Gland*, Sec. 4, Fasc. 15. Washington, DC: Armed Forces Institute of Pathology.
40. Underdahl, L. O., Woolner, B. and Black, B. M. (1953): J. Clin. Endocr., **13**, 20.
41. Moldawer, M. P., Nardi, G. L. and Raker, J. W. (1954): Amer. J. Med. Sci., **228**, 190.
42. Wermer, P. (1963): Amer. J. Med., **35**, 205.
43. Schmid, J. R., Labhart, A. and Rossier, P. H. (1961): *Ibid.*, **31**, 343.
44. Ellison, E. H. (1956): Surgery, **40**, 147.
45. Raker, J. W., Henneman, P. H. and Graf, W. S. (1962): J. Clin. Endocr., **22**, 273.
46. Soffer, L. J., Iannaccone, A. and Gabrilove, J. L. (1961): Amer. J. Med., **30**, 129.
47. McGeown, M. G. and Morrison, E. (1959): Postgrad Med. J., **35**, 330.
48. Danowski, T. S. (1962): *Clinical Endocrinology*, vol. 3. Baltimore: Williams & Wilkins.
49. Randall, R. V. and Keating, F. R. (1958): Trans. Assoc. Amer. Phycns., **71**, 77.
50. Robbins, C. L. (1935): J. Amer. Med. Assoc., **104**, 117.
51. Mather, H. G. (1953): Brit. Med. J., **2**, 424.
52. Lloyd, H. M. and Rose, G. A. (1958): Lancet, **2**, 1258.
53. McGeown, M. G. (1963): Irish J. Med. Sci., **6**, 301.
54. Kleeman, C. R., Rockney, R. E. and Maxwell, M. H. (1958): J. Clin. Invest., **37**, 907.
55. Riddick, F. A. and Reiss, E. (1962): Ann. Intern. Med., **56**, 183.
56. Rasmussen, H. and Craig, L. C. (1958): J. Amer. Chem. Soc., **81**, 5003.
57. Kyle, L. H., Beisel, W. R. and Canary, J. J. (1962): Ann. Intern. Med., **57**, 957.
58. Henneman, P. H., Benedict, P. H., Forbes, A. P. and Dudley, H. R. (1958): New Engl. J. Med., **259**, 802.
59. Bandy, P. K. (1964 - 65): *Year Book of Medicine*, p. 699. Chicago: Year Book Publishers.
60. Beisel, W. R., Gerard, E. S., Barry, K. G., Herndon, E. G. jnr., Meroney, W. H. and Kyle, L. H. (1962): Metabolism, **10**, 771.
61. Nordin, B. E. C. (1962): Scot. Med. J., **7**, 74.
62. Yendt, E. R. and Jaworski, Z. F. (1961): *The Parathyroids*, p. 439. Illinois: Charles C. Thomas.
63. Milne, M. D., Stanbury, S. W. and Thomson, A. E. (1952): Quart. J. Med., **21**, 61.
64. Chambers, E. L., Gordon, G. S., Goldman, L. and Reifenstein, E. C. (1956): J. Clin. Endocr., **16**, 1507.
65. Talpers, S. J. and Stein, J. D. jnr. (1959): Metabolism, **8**, 170.
66. Reynolds, T. B., Lanmon, H. and Tupikova, N. (1960): Arch. Intern. Med., **106**, 48.
67. Thomas, W. C., Connor, T. B. and Morgan, G. H. (1958): J. Lab. Clin. Med., **52**, 11.
68. Nordin, B. E. C. and Fraser, R. (1960): Lancet, **1**, 947.
69. Petit, D. W. and Clark, R. L. (1947): Amer. J. Surg., **74**, 860.
70. Bruce, J. and Strong, J. A. (1955): Quart. J. Med., **24**, 307.
71. Howard, J. E., Hopkins, T. R. and Connor, T. B. (1953): J. Clin. Endocr., **13**, 1.
72. Kyle, L. H., Canary, J. J., Mintz, D. H. and De Leon, A. (1962): *Ibid.*, **22**, 52.
73. Goldsmith, R. S. and Forland, M. (1964): Arch. Intern. Med., **113**, 550.
74. Pronove, P., Bell, N. H. and Bartter, F. C. (1961): Metabolism, **10**, 367.
75. Leading article (1965): Lancet, **1**, 361.
76. Cope, O., Barnes, B. A., Castleman, B., Meuller, G. C. E. and Roth, S. I. (1961): Ann. Surg., **154**, 491.
77. Stanbury, S. W., Lumb, G. A. and Nicholson, W. F. (1960): Lancet, **1**, 793.