PRIMARY HYPERPARATHYROIDISM, NEPHROCALCINOSIS AND RENAL STONE

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According to Albright[1] the presence of the parathyroid glands was not known to the world until 1880, when Sandström[2] began a careful examination of the region around the thyroid gland and named the organs which he found, and described as being the size of a small pea, the glandulae parathyroideae. For a good many years the only significance attached to these glands was their anatomical situation.

Von Recklinghausen's Disease

In a Festschrift published in 1891 in honour of the 71st birthday of Rudolf Virchow, Professor von Recklinghausen,[3] of Strassburg, reported on a series of 16 patients suffering from a variety of bone diseases, of which 3 exhibited bone changes which he described as osteitis fibrosa cystica. Subsequent examination by Albright[1] of the data in connection with these 3 cases has led him to conclude that in fact only one was a true case of osteitis fibrosa cystica and that the other 2 were cases of polyostotic fibrous dysplasia. The historic case was a 40-year-old mason, who in April 1888 fell from a 3-meter-high ladder, sustained a fracture, and was admitted to hospital. While he was in hospital a series of spontaneous fractures occurred, and later he developed widespread excruciating pain in the bones and the most extensive bending of several long bones. He died on 4 October 1889, and post-mortem widespread fibrosis, cysts and giant-cell tumours were found in the bones. In 1933 Jung[4] (quoted by Thannhauser[5]) looked up the original autopsy report on this case at the Pathological Institute of Strassburg and found the following comment: 'Above the left thryoid gland, a lymph gland, red-brown in colour, is present.'

In 1903 Askanazy[6] described a case of von Recklinghausen's disease (osteitis fibrosa cystica) and commented upon the presence of a parathyroid tumour. No special significance seems to have been attached to the association. In 1906 Erdheim,[7] working with parathyroidectomized rats, focused attention on an interrelationship between the parathyroids and calcium metabolism. In 1907 the same worker described enlargement of multiple parathyroids in patients dying of osteomalacia[8] and concluded that the enlargement of the parathyroids in osteomalacia is compensatory. Descriptions of parathyroid hypertrophy in osteomalacia continued, and the same line of thought was applied to findings of parathyroid adenomata in cases of osteitis fibrosa cystica; the possibility was not contemplated at that time that what is true for osteomalacia might not be true for von Recklinghausen's disease.

In 1915 Schlagenhaufer[9] pointed out that in von Recklinghausen's disease of bone the parathyroid enlargement involves only one gland, which would be hard to explain if the hypertrophy were secondary. There, however the matter seems to have rested until, in 1925, Felix Mandl,[10] still acting on the assumption that the parathyroids enlarged to meet the greater demand for calcium, transplanted 4 parathyroid glands into the abdominal wall of a man with generalized osteitis fibrosa. No improvement followed, and he accordingly explored the neck, where he found a parathyroid tumour measuring 2·5 × 1·5 × 1·2 cm. This was removed and the subsequent disappearance of pain in the bones, the reduction of excretion of calcium in the urine, and the general improvement in the patient's health, constituted the first clinical evidence that in this disease the parathyroid lesion is primary and the skeletal changes secondary. In 1926 a diagnosis of hyperparathyroidism was made for the second time, when Du Bois *et al.*[11] finding a raised serum calcium in a case of osteitis fibrosa cystica, made a metabolic study which confirmed the suspicion of hyperparathyroidism. In this case after 6 negative neck explorations a parathyroid tumour was eventually found by splitting the sternum.

Renal Stone

Most of the cases of hyperparathyroidism subsequently reported were in the classic form of osteitis fibrosa cystica. In 1934, however, Albright, Aub and Bauer[12] pointed out that other forms of the disorder exist and are not rare pathological curiosities but conditions that every practitioner may expect to meet. In a study of 17 cases they described 6 clinical types of the condition and concluded that 'from the few patients thus far examined we are induced to believe that hyperparathyroidism will turn out to be a fairly common cause of urinary stone and that in future the case in which there is a stone and no bone disease will be the commoner type of hyperparathyroidism'. As knowledge of the disorder advanced evidence accumulated indicating the importance of the condition to the urologist, and in 1941 Albright[13] confirmed his earlier opinion by reporting that symptoms associated with nephrolithiasis are the commonest first manifestation of hyperparathyroidism. Later reports have fully substantiated this statement. At the Mayo Clinic 15-20 cases of hyperparathyroidism are diagnosed annually and, according to Black[14] (1953), these can be 'attributed almost entirely to a more careful screening of patients with urinary lithiasis for hypercalcaemia'.

In tracing the history of the condition it is both interesting and important to observe how hyperparathyroidism, initially described as a bone disease, has progressed into the sphere of the urologist. A growing proportion of cases are being diagnosed because of renal changes alone and the careful investigation of all cases of renal calculus attending urological clinics is becoming increasingly rewarding in the early diagnosis of hyperparathyroidism.

THE PARATHYROID GLANDS

Anatomy

The parathyroid glands are two pairs of reddish-brown glands each about the size of a small pea and ellipsoid in shape. They are situated usually in relation to the posterior aspect of the thyroid lobes.

The superior gland is fairly constant in position, lying behind the upper third of the lobe and related to the lateral surface of the trachea. It is stated to be invariably between the true capsule of the gland and its fascial sheath.

The inferior gland is situated usually behind the lower part of the lobe, either above or below the inferior thyroid artery as it enters the thyroid substance. Considerable variations, however, exist. The gland may be found behind the oesophagus, either in the neck or in the posterior mediastium, or it may be in the retrosternal space Occasionally it may be situated within the thyroid substance.

The cells are of two types: (1) Chief or non-granular cells with faintly staining nuclei and (2) a few eosinophil cells with well-marked nuclei.

Physiology

The active principle of the parathyroids is parathormone, first isolated by Collip[15] in 1925. The most striking and obvious effect of parathormone is on the level of serum calcium. In health the total serum calcium is between 9 and 11 mg.%. This consists of (*a*) non-diffusible calcium bound to protein, usually 4-5 mg.% and fluctuating according to the level of the serum proteins (McLean and Hastings,[16]) (*b*) calcium ions which are freely diffusible and usually total 4·75-6·25 mg.%, and (*c*) a small unionized but diffusible quantity (0·25 mg.%) of calcium in the form of organic salts such as calcium citrate. The solubility product of calcium and phosphate ions in the serum is constant and this means that a rise in calcium ions leads to a fall in phosphate ions and vice versa. Normally the serum is physically supersaturated with both these ions. This mechanism is controlled by parathormone.

HYPERPARATHYROIDISM

Clinical hyperparathyroidism may result from a localized tumour (adenoma or carcinoma) or diffuse hyperplasia of all the parathyroid glands. The lesion most often causing primary hyperparathyroidism is a single adenoma of one of the glands. This occurred in 84% of the cases described by Hellström[17] in 1954 and in 87% of the cases in Black and Zinner's 1956 series.[18] Adenomas are equally frequent on the right and left sides and are 5 times more common in the lower than the upper glands (Norris[19]). The same observer, in his review of 322 cases in the world literature up to 1947, found that 90% of adenomas are in the upper or lower glands and 10% are aberrant; of the aberrant tumours 63% are mediastinal, 30% within the thyroid gland and 7% behind the oesophagus.

Hellström,[17] in 39 adenomata, found one case with 2 glands involved; 14% of his cases showed primary hyperplasia. Black and Zinner[18] report that primary hyperplasia was found in 10% of their series of 207 cases and when seen it was recognized by enlargement of all the parathyroid glands, the hyperplastic tissue being darker in colour and more lobulated than the usual adenoma. They observed an unusual polyendocrine syndrome in 5 cases, with associated hyperinsulinism and hyperparathyroidism, and (in 3 of the 5) a pituitary tumour also. In this series more than one parathyroid was always involved, and under some circumstances all the glands were involved. Carcinomas of the parathyroid are rare; Gentile *et al.*[20] collected 21 examples from

the literature and Black *et al.*[18] reported an incidence of between 0·5 and 1·0% in their series.

The adenomata are usually well circumscribed, brownish-red in colour and soft in consistency. They vary in diameter from 1 to 3 cm. There is no constant histological pattern. They may be composed of (1) small or large 'chief' cells, which are larger than the corresponding cells of the parathyroid, (2) large water-clear cells, or (3) oxyphil cells. It is common to find a mixture of all cell types.

Hypertrophy of all four glands is usually characterized by a proliferation of water-clear cells only. These are larger than normal, with peripherally placed nuclei. Usually no oxyphil or chief cells can be found.

An overproduction of parathormone by any of the above will produce abnormal physiological and biochemical changes. Briefly these are:

1. Elevation of serum calcium.
2. Increased excretion of calcium in the urine.
3. Increased excretion of phosphate in the urine.
4. Decreased serum inorganic phosphorus.
5. Increase in the serum alkaline phosphatase of the blood.

There are two main theories on the mode of action of the excess of parathormone. Thompson and Collip [21] believe that parathormone stimulates osteoclastic activity which leads to widespread lacunar absorption, the liberated calcium and phosphate being absorbed into the circulation, and the excess being excreted by the kidneys. Jahan and Pitts[22] carried out animal experiments to test this theory and state that the hypercalcaemia (and resultant hypercalciuria) produced by the excess of parathormone are dependent on its extrarenal actions of mobilizing calcium from the body stores and not on any specific depression of renal tubular reabsorption of either calcium or phosphorus. Milne[23] after experimental observations on human calcium metabolism supports this theory and further experimental work to substantiate it has been done by Stewart and Bowen[24] and Talmage *et al.*[25] The second theory is that of Albright,[26] who states that the excess of parathormone affects the renal threshold of serum phosphates so that an excess is excreted in the urine. The fall in serum-phosphate ions results in mobilization of calcium from the bones in order to maintain the solubility product at a constant level. The serum calcium is thus raised and any excess is excreted in the urine.

The bone lesions are the result of decalcification. Renal changes occur in almost every case, but the cause is as yet not established. There appears to be structural or functional tubular damage resulting either from increased excretion of calcium and phosphorus, or a toxic process *via* the parathyroid hormone, or both these factors. Parathormone produces increased serum calcium, but increased serum calcium does not necessarily induce nephrocalcinosis. Engel[27] suggests that parathormone depolymerizes ground substance and thereby increases calcifiability; Baker *et al.*[28] carried out a series of experiments on rats and produced evidence to support this view. The resulting renal changes are interstitial fibrosis, calcification and infiltration by lymphocytes and plasma cells, cystic tubular dilatation, and sometimes calcification of tubular basement membranes and relative absence of active glomerulitis or involvement of tubular epithelial cells. The interstitial calcium deposition is mainly peritubular and is preceded by damage inflicted on kidney tissue. Further damage results from interference with tubular function and tubular obstruction (Anderson[29]).

Clinical Features

Having due regard to the physiological, biochemical and pathological changes it can be seen that the symptoms and signs of hyperparathyroidism can be distributed under three sub-headings:

1. *General.* General symptoms such as lassitude, muscle weakness, nausea or vomiting, and constipation may occur. They have been attributed to the hypercalcaemia (Morele[30]). Various other symptoms have been reported. Hunter and Turnbull[31] noted a diminution in auditory acuity and Simpson[32] reported 5 cases of deafness and 1 of aphonia. Bellin and Gerswhin[33] noted calcification in the ear drums in a patient with hyperparathyroidism. Cogan[34] described calcification in the superficial layers of the periphery of the cornea leading to 'band keratitis'. Fitz and Hallman[35] report the occasional occurrence of psychoses associated with hyperparathyroidism. Cases of intense hypercalcaemia and 'parathyroid poisoning' have been reported (Dawson and Struthers[36]), there being gross metastatic deposit of calcium in almost every organ.

2. *Due to Bone Disease.* Early symptoms of skeletal involvement are bone pain and tenderness. General decalcification of the skeleton eventually leads to deformities and pathological fractures; bone cysts and tumours also appear. Tumours and cysts arise most commonly at the ends of the long bones and in the metacarpals and metatarsals, and bone tumour may be the presenting symptom. They may also occur in the jaw, so that the patient may first present with an epulis. Early bone changes which may be evident on X-ray examination are a 'ground-glass' appearance of the vault of the skull, subperiostial bone absorption in the phalanges of the hands, particularly the middle phalanges, and loss of the lamina dura of the teeth. The bony changes of hyperparathyroidism must be differentiated from those of osteoporosis, osteomalacia, Paget's disease, polyostotic fibrous dysplasia, multiple myeloma, metastatic osseous malignancy. Less common conditions which have at times been confused are xanthomatosis, Gaucher's disease, and benign metastasizing haemangioma.

3. *Due to Renal Disease.* Polyuria and polydipsia, without radiological changes in the kidneys, are often marked clinical features of hyperparathyroidism. These are thought to be due to the increased excretion of calcium and phosphate. Renal colic, parenchymal renal calcification, nephrocalcinosis and renal stone commonly occur.

In 1947 Norris[19] reported that out of a total of 322 cases reviewed by him, only 17 showed nephrocalcinosis or renal stone alone (5%). In 1953 Lahey and Murphy[37] reported 29 cases of hyperparathyroidism of which 4 presented with only nephrocalcinosis or renal stone (14%), Richardson[38] reported 11 cases of which 4 presented with nephrocalcinosis or renal stone alone (36%), and Black[14] reported 112 cases of hyperparathyroidism of which 73 showed only nephrocalcinosis or renal stone (65%). In 1954 Hellström[17] reported 50 cases of which 27 showed only nephrocalcinosis or renal stone (54%). In the latest published series, of 207 proven cases of hyperparathyroidism to 1954 (Black and Zinner[18]), 80% had renal stone or nephrocalcinosis.

It is thus evident that a growing proportion of cases of hyperparathyroidism have been diagnosed because of renal changes alone. These cases have been detected by the careful investigation of renal calculus cases attending urological clinics. It is thus an obligatory routine to test for hyperparathyroidism in every case of nephrocalcinosis or renal stone and experience has shown that this routine must not be confined to multiple, bilateral or recurrent stones.

The percentage of all cases of renal stone which are due to hyperparathyroidism is unknown. Cook and Keating,[39] in 1945, reported that out of 850 cases of renal stone 1·65% had proven hyperparathyroidism. Cope,[40] in 1942, suggested that 10-15% of cases of renal stone eventually showed hyperparathyroidism. Black and Zinner[18] now agree with a possible figure of 5% incidence of hyperparathyroidism among patients having renal stone. Although the commonest cause of nephrocalcinosis (Fig. 1) is hyperparathyroidism, it may also occur in hyperchloraemic acidosis, chronic pyelonephritis, chronic glomerulonephritis,[41] vitamin-D intoxication, milk-alkali (Burnett's) syndrome, sarcoidosis and 'idiopathic' hypercalciuria.

Diagnosis

The final diagnosis of hyperparathyroidism once suspected is made on the biochemical findings. The early and frequent occurrence of renal lesions alone has already been stressed, as has the necessity for full investigation of all cases of renal stone or nephrocalcinosis. The following investigations must be carried out.

1. *Serum Calcium.* The presence of a raised serum calcium is the most important single finding. Several estimations should be carried out at intervals, and repeated over a long period if necessary once the condition is suspected. The readings should be consistent and high figures present no difficulty in diagnosis. Ideally the same biochemist should carry out the estimations and his standard top normal figure should be well established if small rises are also to become of diagnostic value. The serum protein should be estimated simultaneously, since if it is low the serum calcium reading may be normal or low and may conceal an elevated ionic calcium. The chart provided by McClean and Hastings[16] is of value in arriving at the correct figure for the ionic calcium (Fig. 2).

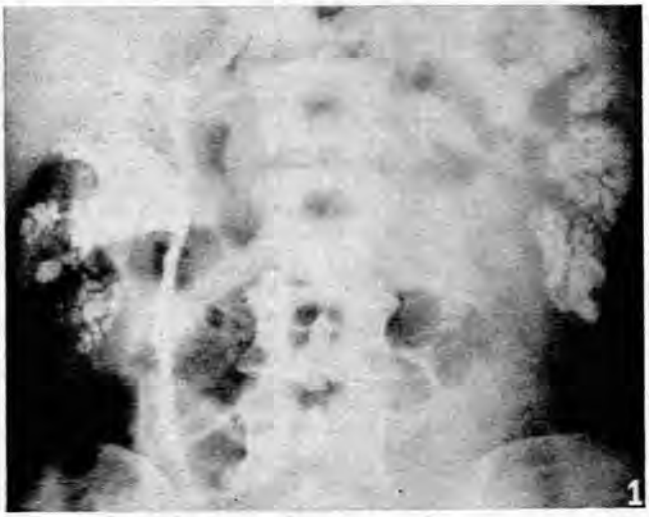

Fig. 1. Nephrocalcinosis.

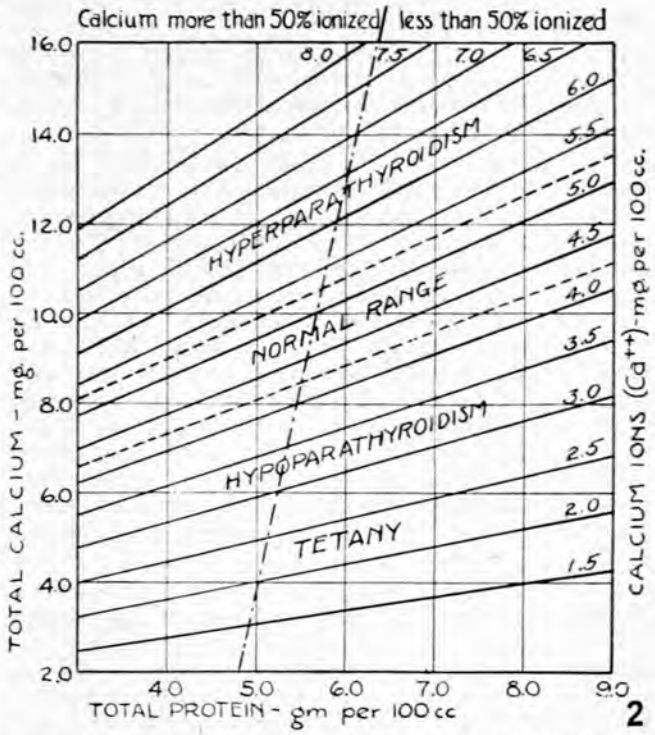

Fig. 2. Chart for calculation of Ca^{++} concentration from total protein and total calcium of serum or plasma (McClean and Hastings,[16] by permission of the American Journal of the Medical Sciences).

2. *Serum Phosphorus.* A low figure for the phosphorus content of the blood, along with a high serum calcium, is strongly suggestive of hyperparathyroidism. A normal or raised figure does not however rule out the possibility, for renal damage may lead to phosphorus retention.

3. *The 24-hour Urinary Calcium.* Figures for the urinary calcium show wide variations. A finding of hypercalciuria on a low calcium diet favours a diagnosis of hyperparathyroidism, but in more than half the cases examined by Hellström[17] the urinary calcium was within normal limits. Hypercalciuria also occurs in many other conditions.[42]

4. *Serum Alkaline Phosphatase.* This is raised only if there are skeletal changes, and such a finding should stimulate a careful radiological search of the skeleton. Early bone changes are found in the skull, the phalanges of the hands and the teeth (as mentioned in a previous paragraph) and these sites should be examined first.

Hypercalcaemia thus emerges as the most important diagnostic feature. It has also been described in (1) metastatic osseous malignancy, (2) multiple myeloma, (3) sarcoid, (4) the milk-alkali (Burnett's) syndrome and (5) vitamin-D intoxication; conditions (1), (2) and (3) have bone lesions which are occasionally difficult to differentiate from those of hyperparathyroidism, and conditions (3), (4) and (5) may present with nephrocalcinosis or renal stone.

Differential Diagnosis

Metastatic Osseous Malignancy. Malignant secondary invasion of bone may give rise to hypercalcaemia. A primary source should be sought for in the common sites, viz. breast, prostate, kidneys, bronchus and thyroid.

Multiple Myeloma. The serum phosphorus is usually normal or raised in multiple myelomatosis, but Snapper[42] reported a case with a low serum phosphorus. Renal damage may lead to phosphorus retention in hyperparathyroidism. Serum phosphorus readings may thus be of little help in the differential diagnosis. Bence-Jones protein has been found in the urine in less than half of the cases of myeloma and when it occurs it may be continuous or periodic, and in scanty or large amounts. Bence-Jones proteinuria may also occur in myxoedema, leukaemia and carcinoma. The serum alkaline phosphatase, however, is usually normal in multiple myeloma. An increase in the plasma proteins, particularly affecting the globulins, is characteristically found in many cases of multiple myelomatosis. A bone-marrow biopsy with the demonstration of an increased number of plasma cells would confirm the diagnosis.

Sarcoid. Bone lesions, when present, are in the nature of circumscribed lesions of coarse trabeculation and sharply punched out small cyst-like areas, chiefly in the hands and feet. Harrel and Fisher[43] found that hypercalcaemia was not confined to cases with bone disease. Difficulty is mainly encountered in the cases in which there are only metabolic changes and there is an obscure hypercalcaemia. Serum phosphorus estimations may be equivocal. Dent's cortisone test[44] is a valuable diagnostic aid in both this condition and *vitamin-D intoxication.* In this test 150 mg. of cortisone are given for 10 days and the serum calcium is estimated on the 5th, 8th and 10th days. The hypercalcaemia of sarcoidosis will rapidly fall, usually to normal levels, during this time, as will that of vitamin-D intoxication.

Milk-alkali (Burnett) Syndrome.[45] In this condition there is a history of prolonged and excessive intake of milk and absorbable alkali. There is hypercalcaemia without hypercalciuria or hypophosphataemia. The serum alkaline phosphatase is normal and there is a mild alkalosis. Calcinosis is present, manifested especially by an ocular lesion resembling band keratitis. The history is the most important factor in the differential diagnosis. After withdrawal of milk and alkali powders an improvement in the clinical state results and the hypercalcaemia often diminishes.

Treatment

Surgical removal of the affected gland or glands will normally bring about a complete cure of hyperparathyroidism. Exploration of the neck is indicated when the diagnosis of hyperparathyroidism has been confirmed by the biochemical findings. It is highly unlikely that any swelling of the affected glands can be detected on clinical examination. It is rarely necessary to do more than the standard neck dissection with careful identification of the parathyroid glands. Methodical identification of each of the four glands is the method of choice. If no tumour is found in the normal situations of the glands, the search should be extended into the upper part of the thorax, splitting the sternum if necessary The retrosternal and retro-oesophageal spaces should both be explored and a branch of the inferior thyroid artery running downwards into the thorax may point the way to a parathyroid tumour. Rarely the affected parathyroid may be buried within the thyroid substance. If exploration of the thyroid confirms this, the tumour may be enucleated or subtotal thyroidectomy performed. In the absence of a tumour, if demonstrable hyperplasia of all the glands is found three should be resected.

After operation an immediate fall occurs in the urinary calcium and phosphorus excretion. The level of calcium in the serum falls to normal within 1-4 days. When bone disease is present operation is sometimes followed by a fall of serum calcium to sub-normal levels as the decalcified bones absorb calcium from the plasma, the remaining parathyroid tissue being insufficient to prevent this reversal. In some cases the fall of the serum calcium to subnormal limits progresses to the point of tetany. Parenteral administration of calcium salts is required. It can be given either intramuscularly or intravenously, usually in the form of the gluconate. Parathyroid hormone and calciferol or dihydrotachysterol, used effectively and logically in tetany which follows damage to the parathyroid glands in the course of thyroidectomy, are relatively ineffective in this condition.

SUMMARY

The history of primary hyperparathyroidism is presented. Initially described in its classic form of osteitis fibrosa cystica only, its gradual recognition as a disease of major importance to the urologist is outlined.

The anatomy, physiology and pathology of the parathyroid glands and the clinical features, diagnosis and treatment of primary hyperparathyroidism are discussed.

The high proportion of patients with hyperparathyroidism presenting with renal changes alone is emphasized.

The careful investigation of all patients with nephrocalcinosis or renal stone for hyperparathyroidism is stressed as an obligatory routine—not only in cases where the stones are multiple, bilateral or recurrent.

Hypercalcaemia is considered to be the most important single diagnostic feature. Its possible causes are discussed.

REFERENCES

1. Albright, F. (1948): J. Clin. Endocr., **8**, 637.
2. Sandström, I. (1880): Upsala LäkForen. Förh, **15**, 441.
3. Von Recklinghausen, F. D. (1891): Festschrift Rudolf Virchow, Berlin.
4. Jung, E. (1933): Congrès franç. Chir., **42**, 200.
5. Thannhauser, S. J. (1944): Medicine, **23**, 105.
6. Askanazy, M. (1904): Arb. path. Anat. Inst. Tubingen, **4**, 398.
7. Erdheim, J. (1906): Mitt. Grenzgeb. Med. Chir., **16**, 632.
8. Erdheim, J. (1907): S.B. Akad. Wiss. Wien, **116**, 311.
9. Schlagenhaufer (1915): Wien. klin. Wschr., **28** (2), 1362.
10. Mandl, F. (1926): Arch. klin. Chir., **143**, 245.
11. Hannon, R. R., Shorr, E., McClellan, W. S. and Du Bois, E. F. (1930): J. Clin. Invest., **8**, 215.
12. Albright, F., Aub, J. C. and Bauer, W. (1934): J. Amer. Med. Assoc., **102**, 1276.
13. Albright, F. (1941): *Ibid.*, **117**, 527.
14. Black, B. M. (1953): *Hyperparathyroidism.* Springfield, Ill.: C. C. Thomas.
15. Collip, J. B. (1925): J. Biol. Chem., **63**, 395.
16. McClean, F. C. and Hastings, A. B. (1935): Amer. J. Med. Sci., **189**, 601.
17. Hellström, J. (1954): Acta endocr., **16**, 30.
18. Black, B. M. and Zinner, J. F. (1956): Arch. Surg., **72**, 830.
19. Norris, E. H. (1947): Int. Abstr. Surg., **84**, 1.
20. Gentile, R. J., Skinner, H. L. and Ashburn, L. L. (1941): Surgery, **10**, 793.

21. Thompson, D. L. and Collip, J. B. (1932): Physiol. Rev., **1,** 309.
22. Jahan, I. and Pitts, R. F. (1948): Amer. J. Physiol., **155,** 42.
23. Milne, M. D. (1951): Clin. Sci., **10,** 471.
24. Stewart, G. S. and Bowen, H. F. (1952): Endocrinology, **51,** 80.
25. Talmage, R. V., Kraintz, F. W., Frost, R. C. and Kraintz, L. (1953): *Ibid.*, **52,** 322.
26. Albright, F. and Reifenstein, E. C. (1948): *The parathyroid glands and metabolic bone disease.* London: Baillière, Tindall and Cox.
27. Engel, M. B. (1951): Arch. Path., **53,** 339.
28. Baker, R., Reaven, G. and Sawyer, J. (1954): J. Urol., **71,** 511.
29. Anderson, W. A. D. (1939): Endocrinology, **24,** 372.
30. Morele, J. (1932): J. Chir. (Brux.), **31,** 381.
31. Hunter, D. and Turnbull, H. M. (1931): Brit. J. Surg., **19,** 203.
32. Simpson, J. A. (1954): Brit. Med. J., **1,** 494.
33. Bellin, D. E. and Gerswhin, B. S. (1935): Amer. J. Med. Sci., **190,** 519.
34. Cogan, O. E. (1947): Unpublished data cited in Albright and Reifenstein, **26,**
35. Fitz, T. E. and Hallman, B. L. (1952): Arch. Intern. Med., **89,** 547.
36. Dawson, J. W. and Struthers, J. W. (1923): Edinb. Med. J., **30,** 421.
37. Lahey, F. H. and Murphy, R. (1953): Surg. Clin. N. Amer., **33,** 723.
38. Richardson, J. E. (1953): Ann. Roy. Coll. Surg. Engl., **13,** 100.
39. Cook, E. N. and Keating, F. R. (1945): J. Urol., **54,** 525.
40. Cope, O. (1942): J. Missouri. Med. Assoc., **39,** 273.
41. Arons, W. L., Christensen, W. R. and Sosman, M. C. (1955): Ann. Intern. Med., **42,** 260.
42. Modlin, M. (1957): S. Afr. Med. J., **31,** 1010.
43. Snapper, I. (1948): J. Mt. Sinai Hosp., **15,** 156.
44. Harrell, G. T. and Fisher, S. (1939): J. Clin. Invest., **18,** 687.
45. Dent, C. E. (1956): Brit. Med. J., **1,** 230.
46. Burnett, C. H., Commons, R. R., Albright, F. and Howard, J. (1949): New Engl. J. Med., **240,** 787.