

PRIMARY HYPERPARATHYROIDISM

Report of 10 Cases

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Primary hyperparathyroidism is a clinical entity caused by an excessive production of parathyroid hormone which may result from an adenoma of one or more of the parathyroid glands or from hypertrophy of all four parathyroid glands. This excess is considered the essential abnormality in hyperparathyroidism because the parathyroid hormone has a profound and wide-spread effect upon the metabolism of calcium and phosphorus. A variety of complications can occur which may so dominate the clinical picture as to detract attention from the primary source of the disease. Milder forms of the disease may completely escape attention and lead to fatal renal damage. Hyperparathyroidism in its most typical form presents hypercalciuria, hypercalcemia, hyperphosphaturia, and hypophosphatemia. When extensive skeletal involvement is present high levels of alkaline phosphatase may also be observed.

In presenting our observations of 10 patients with primary hyperparathyroidism, we wish to re-emphasize some of the more salient features of the clinical syndrome. The diagnosis, as in other better known nutritional and metabolic diseases, frequently depends upon the recognition of one or more of the complications. Because of the variable types of symptoms the patient may present himself to the urologist, orthopedist, neurologist, gastroenterologist, dentist, surgeon, or internist.

The diagnosis of parathyroid adenoma was made in this Clinic only once prior to 1940. In the past eighteen months it has been made eight times. The work of Albright^{1,2} and the reports of Keating and Cook³ and our own experience have convinced us that the disorder occurs much more frequently than the number of diagnoses would seem to indicate. A clear recognition of the possible complications and an accurate estimation of serum calcium and inorganic phosphorus levels are essential in arriving at a diagnosis in suspected cases.

Case Reports

Case 1. A woman, aged 64, complained of weakness, anorexia, nausea and vomiting, constipation, headache, skeletal pains, and attacks of renal colic and urinary tract infection which had covered a period of thirteen years. Polyuria had appeared as a late symptom. The patient also had severe hypertension with cardiac hypertrophy and dependent edema. A small nodule was present in the region of the left lobe of the thyroid.

Roentgenograms demonstrated bilateral renal calculi, demineralization of the bones of the spine and pelvis, and cystic areas in several ribs and in the left tuber ischii. Serum calcium was 14.3 (normal 9-10.5), serum inorganic phosphorus 1.7 mg. per cent (normal 2.5-4), and alkaline phosphatase 7 Bodansky units. Urea clearance was 36 per cent in the first hour and 38 per cent in the second hour.

At operation on July 25, 1935, a yellowish tumor measuring $2.7 \times 2.0 \times 1.5$ cm. was removed from the right tracheo-esophageal groove and proved to be a chief cell adenoma. The nodule palpated preoperatively was a thyroid adenoma. Postoperative tetany occurred with total serum calcium as low as 5.7 mg. and phosphorus as high as 6.2 mg. per cent. The patient continued to complain of skeletal pains, which appeared to be of nerve root origin. There was slight improvement of renal function postoperatively, and blood pressure was maintained at distinctly lower levels during a two-year period of observation.

Case 2. A boy, aged 17, was first seen in October, 1942, complaining of increased salivation. Weakness had been present for two years and was followed by ptyalism, polyuria, a firm swelling of the lower jaw, and a pathologic fracture of the left leg which, though healed for over a year, was disabling because of residual pain. Objectively, there was marked muscular hypotonia, a large epulis of the left mandible, and a nodule which could be palpated and moved with the left lobe of the thyroid. X-ray examination demonstrated extensive skeletal decalcification, bowing of the right femur (fig. 1a), bilateral coxa vara, multiple cystic formations in ribs, both radii, left mandible (fig. 2a), and left tuber ischii, and complete absorption of the periodontal membrane (fig. 2b). Serum calcium was 17.8 mg., phosphorus 2.8 mg. per cent, and alkaline phosphatase

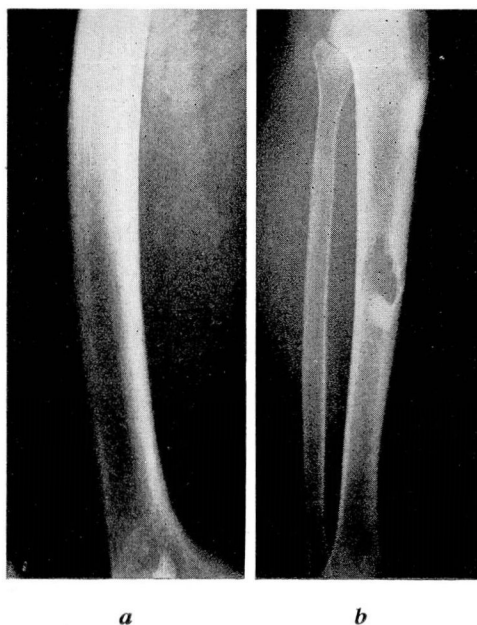


FIG. 1. Case 2. (a) Demonstrating bowing and demineralization of femur.
Case 4. (b) Cyst of tibia; biopsy typical of giant cell tumor.

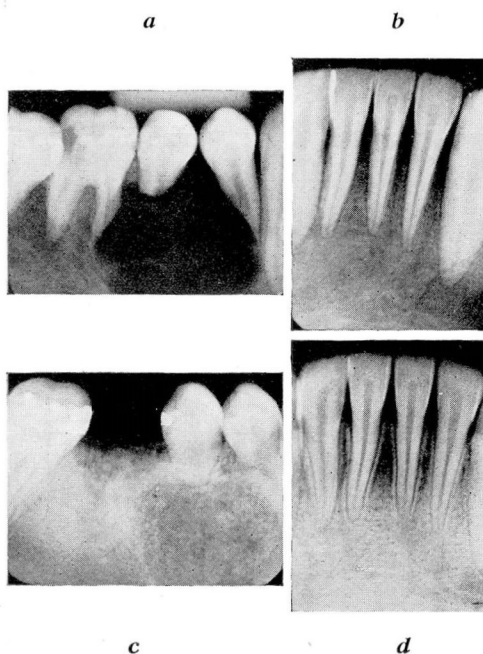


FIG. 2. Case 2. (a) Showing cyst of mandible and (b) absence of periodental membrane. (c & d) Five months after operation, showing healing of cyst and restoration of periodental membrane.

27.4 Bodansky units. Total serum protein was 6.7 Gm. per 100 cc., blood urea measured 39 mg. per cent, carbon dioxide combining power was 36.5 volumes per cent, and urea clearance was 39 per cent in the first hour and 33 per cent in the second hour. The yellowish-brown adenoma removed at operation on October 19, 1942, weighed 18 Gm. with overlying thyroid tissue, measured 3.5 x 3 x 2 cm., and was composed principally of chief cells. The patient developed postoperative tetany and massive hypoproteinemic edema. His bones showed marked recovery after six months (fig. 2 c & d), and he walked well eight months after operation. There was only slight improvement in renal function.

Case 3.* A woman, aged 40, was first seen in September, 1943, complaining of tumors of the jaw of seven years' duration. More recent symptoms included drowsiness, headache, constipation, right lumbar pain, and dysuria. There was also a history of an adequately treated luetic infection. The diagnosis of hyperparathyroidism with osteitis fibrosa cystica and renal calculi had been made at another institution in 1940. At that time serum calcium measured 14.8 mg., phosphorus 1.9 mg. per cent, and alkaline phosphatase 7.6 units. Examination was normal except for large nontender bony swellings of the mandibular rami with extension into the alveolar arch, and tenderness over the right costovertebral angle. X-ray examination showed the mandibular rami to be expanded by a sharply demarcated osteolytic process containing calcific trabeculations (fig. 3). Pyelograms demonstrated calculi in an anomalous right kidney. Smaller calcifications outside of the renal area were suspected to be gallbladder calculi. Serum

* Previously reported by Dinsmore and Zidd.⁴

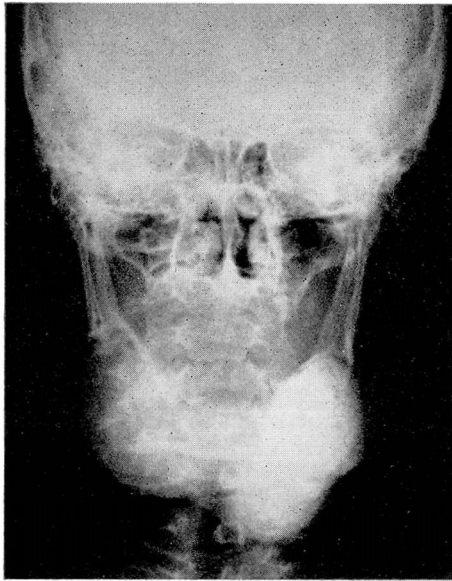


FIG. 3. Case 3. Multiple cysts of mandible.

calcium was 11.8 mg., phosphorus 2.1 mg. per cent, and alkaline phosphatase 1.2 units. At operation on November 8, 1943, a brownish-red ellipsoid 0.3 x 0.4 x 0.8 cm. was removed from behind the left lower pole of the thyroid. Microscopic examination showed it to be composed of pale oxyphil cells with smaller numbers of clear cells and transition clear cells. Eleven months after operation, headaches and drowsiness were completely relieved and the calcium and phosphorus levels were within normal range.

Case 4. A woman, aged 37, was first seen in January, 1945, complaining of sensitivity of the legs, unsteadiness of gait, and difficulty in changing position in bed. Residual pain followed any form of pressure over the body, and the patient stated that at times her bones felt as though they "were chipped away". These symptoms were of two years' duration. She had passed a renal calculus six years previously but had had no subsequent urinary tract symptoms. Slight tenderness to pressure could be elicited over the superficial bony structures. Roentgenograms revealed osteoporosis of the skull and cystic changes in the right ulna, right ilium, greater trochanter and neck of the left femur, both tibiae (fig. 1b), and right fifth metatarsus. A biopsy from the left tibia demonstrated a benign giant cell tumor. The serum calcium was found to be 9.7 mg. and phosphorus 3.4 mg. per cent. Subsequent studies revealed levels of 13.3 and 2.1 mg., respectively, and an alkaline phosphatase of 10.1 units. The Sulkowitch test was strongly positive. Total serum protein was 6.9 Gm. per 100 cc.

The patient was operated upon on March 6, 1945, and a reddish-brown tumor 2.7 x 1.0 x 1.2 cm. in size was removed from beneath the inferior thyroid artery. The cellular structure was primarily a transition clear cell adenoma. Tetany was encountered in the postoperative period and controlled by oral administration of calcium lactate and vitamin D, which was discontinued after three months. Five months after operation the patient stated that she felt better than at any time in the preceding five years.

Case 5. A man, aged 62, was first seen in April, 1946, because of headache, fatigue, dependent edema, and dyspnea. He had had pain in the right flank, and a calculus had been present in the right kidney for sixteen years. Examination revealed cardiac enlargement with blood pressure of 208 systolic and 140 diastolic, a soft aortic systolic murmur, and slight edema of the ankles. Pycelograms disclosed a large calculus in the right renal pelvis and hydronephrosis. The Sulkowitch test was strongly positive. Serum calcium was 12.4 mg., phosphorus 2.4 mg. per cent, and total serum protein 6.4 Gm. per 100 cc. Urea clearance values were within normal limits. Exploration of the neck was performed in August, 1946, by Dr. Robert C. Austin of Dayton, Ohio, who removed a parathyroid adenoma slightly more than 1 cm. in diameter from the left side. The patient survived a myocardial infarction in the immediate postoperative period but was never in good health thereafter. He finally succumbed to a second infarction in December, 1946.

Case 6. A man, aged 27, was first seen in June, 1946, with ureteral colic of three weeks' duration. A calculus was passed following ureteral manipulation. There were no significant physical findings, and pycelograms were negative. Dental films demonstrated

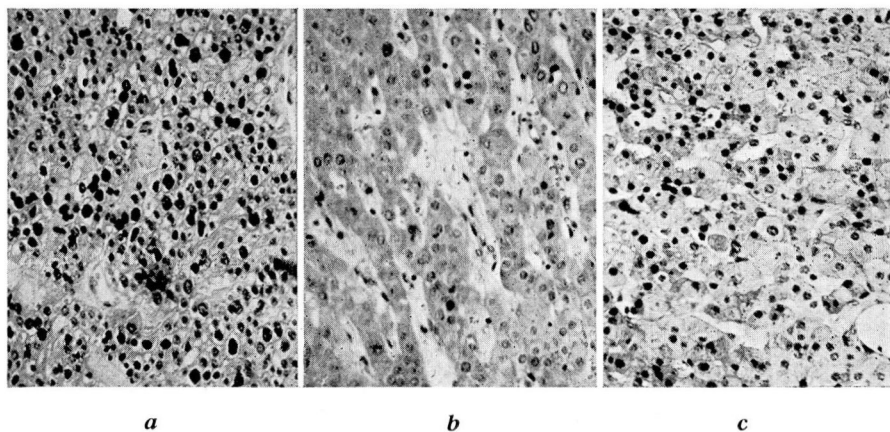


FIG. 4. Case 7. (a) Chief cell adenoma. Case 9. (b) Dark oxyphil cell adenoma. (c) Dark oxyphil cell adenoma occurring in second cousin once removed.

complete absence of the lamina dura around many teeth. The Sulkowitch test was strongly positive. Serum calcium was 13.4 mg., phosphorus 2.0 mg. per cent, and total serum protein 7.0 Gm. per 100 cc. Alkaline phosphatase was 2.4 units.

An exploration of the neck was performed on June 28, and one normal parathyroid gland was removed. Six weeks later the patient complained of weakness, anorexia, polyuria, and polydipsia. He was given a course of deep x-ray therapy to the neck without benefit, following which mediastinal exploration was advised. He returned to his home in St. Louis, and on December 28 an adenoma 1 cm. in diameter was removed from the superior mediastinum at Barnes Hospital. Mild tetany was reported in the postoperative course. Sections of the specimen received from Barnes Hospital showed it to be composed primarily of chief cells.

Case 7. A man, aged 43, was seen in August, 1946, with a history of recurrent renal colic of fifteen years' duration. A right ureterolithotomy had been performed in this institution in 1935, and a left nephrolithotomy had been performed elsewhere in 1942.

Physical examination showed no significant abnormalities. Bilateral renal calculi were demonstrated radiographically, but no osseous abnormalities were found. The Sulko-witch test was strongly positive. Serum calcium was 13.7 mg., phosphorus 2.2 mg. per cent, and total serum protein 7.6 Gm. per 100 cc. A left uretero-meatotomy was performed in September, 1946. A few days later a soft purplish-red adenoma measuring 2.5 x 1.3 x 0.7 cm. was removed from a retrotracheal position beneath the branches of the recurrent laryngeal nerve. The cytology of the sections showed chief cells (fig. 4a) for the most part. The patient passed several more urinary calculi after leaving the hospital. His convalescence was otherwise uneventful.

Case 8. A woman, aged 59, was first seen in September, 1946, with a history of repeated attacks of renal colic during the preceding five years. Bilateral renal calculi had been demonstrated two years previously, when a right nephrolithotomy had been performed. Except for decreased endurance, there were no complaints which were not directly attributable to the renal calculi. Physical examination revealed a state of poor nutrition and a moderate dorsal kyphosis. Urograms demonstrated multiple bilateral renal calculi with pronounced right hydronephrosis. Serum calcium was 12.1 mg.,

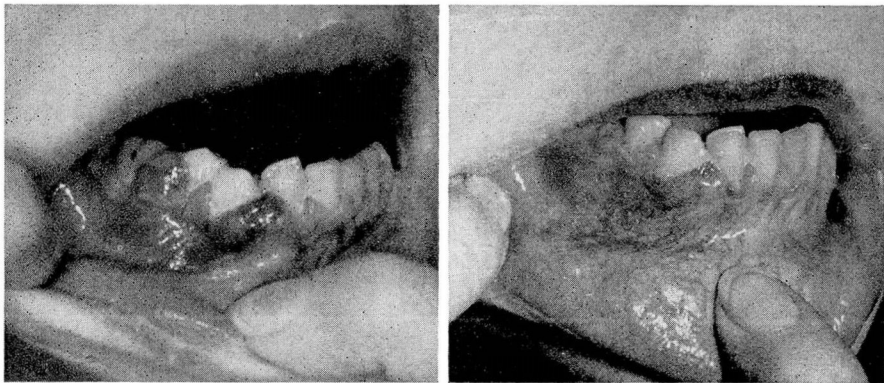


FIG. 5. Case 9. (a) Demonstrating epulis formation. (b) Showing degree of restoration eight weeks after operation.

phosphorus 2.2 mg. per cent, and total serum protein 7.3 Gm. per 100 cc. The Sulko-witch test was strongly positive. Urea clearance was found to be 36 and 38 per cent respectively at one and two-hour intervals. A left pelviolithotomy was performed on September 26, with the extraction of four calculi and evacuation of about 50 cc. of creamy pus. The patient returned for exploration of the neck on May 20, 1947, when a reddish-brown adenoma was removed from near the left inferior pole of the thyroid gland. This measured 3.0 x 1.5 x 1.0 cm. and was composed principally of chief cells. The Sulkowitch test was negative five hours after operation. The patient was reported to be feeling well two months after operation.

Case 9. A woman, aged 20, was first seen in January, 1947, complaining of "lumps" in the mouth. She was nearly three months pregnant. Three areas of gingival swelling had appeared in the preceding nine months, and several teeth had become loosened. She had also experienced weakness and dull aching pains in the legs and had increasing

thirst with polyuria. A small goiter had been gradually enlarging for two years. Family history disclosed that a second cousin once removed had had polycystic bone disease with removal of a parathyroid adenoma in 1942.

Examination disclosed moderate-sized epulides of the left upper and right lower jaw with loosening of adjacent teeth (fig. 5a), a walnut-sized nodule within the left lobe of the thyroid, engorgement of the breasts, and uterine enlargement consistent with ten to twelve weeks' gestation. Roentgen examination revealed a small cystic area above the left acetabulum and multilocular cyst formation of the right mandible with generalized demineralization of the alveolar bone and loss of the lamina dura. The Sulkowitch test was strongly positive, hemoglobin was 10 Gm. (65 per cent), the red blood cell count was 3,830,000, serum calcium 18.3 mg., phosphorus 2.0 mg. per cent, and alkaline phosphatase 4.2 units. Total serum protein was 6.2 Gm. per 100 cc.

At operation on January 22, 1947, a light brownish adenoma measuring 2.2 x 2 x 1.2 cm. and weighing 8.5 Gm. was removed from the substance of the left lobe of the thyroid. This proved to be primarily a dark oxyphil cell tumor (fig. 4b). It is of interest to note that sections of the parathyroid tumor removed from this patient's cousin revealed a mass made up mainly of cells of the same type (fig. 4c).

Mild but readily controlled tetany occurred after operation. The epulides decreased rapidly in size (fig. 5b) and could not be detected after three months. Pregnancy progressed normally to term and a 7-pound male infant was delivered on July 24. There was no evidence of tetany in the child. Studies of the bones have not been made. The patient has felt well since delivery, and the hemoglobin has been maintained at 80 per cent through the use of parenterally administered liver extract.

Case 10. A man, aged 57, was first seen in June, 1947, with a history of bilateral flank pain, recurrent hematuria, and repeated passing of gravel and calculi during the preceding eight years. He had experienced progressive muscular weakness, had become increasingly constipated, and recently had been subject to frequent attacks of postprandial nausea and vomiting associated with persistent dull pain in the right upper abdominal quadrant and right infrascapular region. No jaundice was noted. In addition it was reported that all teeth had become loosened and had been extracted four years previously. Roentgenologic studies demonstrated several calcified gallstones and multiple calculi in an enlarged nonfunctioning right kidney. Cystoscopic examination demonstrated an infected hydronephrosis secondary to ureteral obstruction. Initial serum calcium and phosphorus levels were 13.0 and 3.9 mg. per cent, respectively. Total serum protein was 6.5 Gm. per 100 cc. Blood urea was 114 mg. per cent, and the urea clearance test revealed 21 per cent clearance in the first hour and 17 per cent clearance in the second hour. Following the release of the ureteral obstruction on the right side, the renal status was sufficiently improved to permit exploration of the neck on July 24, 1947, when a yellowish-brown parathyroid adenoma 2 x 1.5 x 1 cm. and weighing 2.2 Gm. was removed from beneath the lower aspect of the left lobe of the thyroid gland. Histologically this was described as a chief cell adenoma with rare pale oxyphil islands. There was no postoperative tetany. The lowest serum calcium level of 8.2 mg. per cent and a phosphorus level of 2.4 mg. per cent were recorded on the sixth postoperative day. Tetany was not observed. The patient recently returned to the hospital and a right pelviolithotomy was performed.

Discussion

There are a number of symptoms and observations which should suggest the possibility of hyperparathyroidism. The symptoms can be divided into three main groups.

Group 1. Those due to hypercalcemia. These consist principally of muscular weakness and decreased muscular excitability. The muscles are frequently flaccid and opposite in type from those of tetany. This particular finding was present in all but 1 of our patients. Constipation is common, and nausea and vomiting may occur. At times symptoms may resemble duodenal ulcer. Polydipsia and polyuria occur frequently and may be sufficiently severe to simulate diabetes insipidus. One-half of the present series of patients noted polydipsia and polyuria. It has been suggested that when polydipsia is a prominent symptom kidney stones are less likely to develop. Ptyalism has been referred to as a complaint and was noted in 1 patient in the present series.

Group 2. Symptoms referable to the urinary tract. These are the commonest first manifestations of the disease. In 8 of 10 patients there was a history of renal colic; 6 had roentgenologic evidence of renal calculi. In 4 there was a history of bilateral renal colic and in 3 roentgen evidence of bilateral stones.

Group 3. Symptoms referable to the skeletal system. Almost any symptom related to the skeletal system may be due to underlying hyperparathyroidism. Ill-defined skeletal pain was present in 4 of our patients. Epulides were present in 2 patients, both of whom had loose teeth. Pathologic fracture and bowing of the femurs occurred in 1 and kyphosis in another. A giant cell tumor was found in 1 patient, indicating that such a finding in others should suggest hyperparathyroidism as the underlying cause. Roentgen diagnosis of osteitis fibrosa cystica was made in 5 of the 10 patients. Resorption of the lamina dura was observed in 4 cases of this series. Dental films were not made in the remaining 6.

The electrolyte imbalance has been corrected in all patients by removal of the parathyroid adenomata. Partial disability remained in some, due to renal calculi or parenchymal renal damage.

In 4 of the 10 patients the tumors were aberrant in location. One was found in the mediastinum at the level of the second rib, two were located in the substance of the thyroid and apparently took origin from the left superior gland, and in the fourth case the tumor arose from the left inferior gland between the esophagus and the trachea. Of the six remaining adenomata one arose from the right inferior and five from the left inferior parathyroid. Two were palpable prior to operation. Of the ten removed, only one occurred on the right side.

On histologic examination six adenomata were described as being composed principally of chief cells. One specimen was identified as a transition clear cell type, one as a pale oxyphil, one as a dark oxyphil,

and in the tenth case no sections were available for study. Serial sections were not made in any case, and in studying the routine sections a few of almost any of the recognized cell types of normal parathyroid gland could be identified in almost every slide. However, in each instance a single cell type could be said to predominate, and in the case of the dark oxyphil cell tumor this predominance was most pronounced. It is noteworthy that an example of this rare type of adenoma was functionally active, for of the four oxyphil cell adenomata found by Norris⁵ in a recent survey of 322 adenomata, only one was accompanied by manifestations of hyperparathyroidism.

Although hyperparathyroidism is generally more common in women,⁵ in this small series the cases were equally distributed between women and men. The disease was accompanied by pregnancy in 1 instance. Five patients had had symptoms for five years or longer; the shortest history was of three weeks' duration and the longest of sixteen years'.

Hyperparathyroidism in its most typical form presents a high blood calcium, high urine calcium, low blood phosphorus, high urine phosphorus, and when there is active extensive skeletal involvement a high alkaline phosphatase. The disease, however, occurs in every degree of severity, and it becomes important to recognize the milder forms, since they may prove fatal. It is well to remember that single serum calcium levels may be normal. One patient in the present series had an initial serum calcium level of 9.7 mg. per cent, although subsequent determinations were high. It is also important that total serum protein be measured, since a normal serum calcium and a low serum protein is abnormal, and a high total protein may explain a high blood calcium due to multiple myeloma or sarcoidosis rather than to parathyroid disease. The nomogram of McLean and Hastings⁶ presents a convenient means of estimating the quantity of ionic calcium present whenever abnormal total proteins are encountered. Hypervitaminosis D must also be considered in the differential diagnosis. In the present group of patients there was no correlation between the degree of hypercalcemia and the duration of the disease or the renal and bone complications.

Serum phosphorus is almost invariably below 3 mg. per cent in hyperparathyroidism unless renal failure is also present. In a normal person a single serum phosphorus level may be low, but in hyperparathyroidism it is consistently low. Low serum phosphorus determinations should receive a great deal more emphasis and hyperparathyroidism be strongly suspected when they are found.

A number of cases of hyperparathyroidism¹ have been reported with normal serum calcium and repeatedly low serum phosphorus levels

prior to operation. Low serum phosphorus levels characterize this group of cases, and in the majority the levels were below 2.5 mg. per cent. In a few instances where renal insufficiency was also present blood phosphorus levels were normal.

In a small group of patients extensive renal damage results from diffuse parenchymal calcinosis. None of this type was clearly defined among the present group of patients, although in 2 there was distinct lowering of renal function, as measured by the urea clearance test, that could not be attributed to other etiologic factors. Only slight improvement of renal function was observed in 1 of these patients over a two-year follow-up period. In the event of renal failure one is likely to encounter phosphorus retention with a reciprocal lowering of calcium and therefore an erasure of the diagnostic biochemical values. Likewise, one should remember that diffuse parathyroid hyperplasia may be the physiologic result of the attempt to overcome the elevated blood phosphorus in certain cases of chronic renal failure and may sometimes be associated with extensive skeletal changes such as may be seen in renal rickets.

Calcium and phosphorus excretion in the urine are both increased in hyperparathyroidism. The degree of phosphaturia in a normal person can be influenced by so many physiologic factors that its study is of little practical value in the recognition of any disease. Furthermore, hypercalciuria occurs in many diseases which do not involve the parathyroid, and since there is some overlapping between normal and mildly hyperparathyroid states in the amount of calcium lost in the urine, this observation also requires careful interpretation. In general, however, hyperparathyroidism is associated with well-marked increase in calcium excretion in the urine. It can be roughly measured with ease by means of the Sulkowitch test. This test consists of the addition of an equal volume of Sulkowitch reagent⁷ to the urine to determine the speed and degree of precipitation of a milky precipitate of calcium oxalate. In our patients in which this test was used a decided degree of hypercalciuria was present. High levels of serum phosphatase are present only if the hyperparathyroidism leads to bone disease, which it frequently does not. An elevation of alkaline phosphatase in hyperparathyroidism has been considered an index of the extent of skeletal decalcification associated with active bone healing and, when present preoperatively, is likely to be accompanied by tetany in the postoperative period. It seems logical to assume that postoperative tetany will occur in those patients having the more calcium-depleted bone.

Three patients presented an elevated alkaline phosphatase preoperatively. They all had roentgen evidence of extensive skeletal de-

calcification, and all developed varying degrees of postoperative tetany which required active medical treatment. Two other patients presented mild degrees of postoperative tetany and did not have an elevated alkaline phosphatase or roentgen evidence of skeletal decalcification prior to operation. Postoperative tetany in 1 of these may have been due to the removal of a normal parathyroid at the first exploration. In the other patient pregnancy complicated the disease and may have had a bearing upon the appearance of postoperative tetany.

The total serum protein levels were well within normal range in 8 patients in this series, and in the first 2 serum protein analyses were not included. Determinations were helpful only in the exclusion of hypercalcemia of nonparathyroid origin. Urea clearance values were an aid in interpreting the preoperative levels of serum phosphorus. Severe secondary anemia out of proportion to the amount of demonstrable kidney damage was present in 1 patient. It has been pointed out that severe hypochromic anemia in the absence of renal failure may accompany hyperparathyroidism due to extensive fibrosis of the bone marrow.²

Conclusions

1. Ten proved cases of hyperparathyroidism associated with parathyroid adenomata have been presented.
2. Attention has been directed to a functioning oxyphil cell adenoma and the unusual occurrence of the same type of tumor in a blood relative.
3. Hyperparathyroidism is to be suspected in the presence of (1) calcific renal calculi, especially when associated with unexplained polydipsia or polyuria, (2) pronounced muscular weakness of indeterminate causes, (3) polycystic bone disease or giant cell tumors of the bone, and (4) unexplained hypercalciuria.
4. In the differential diagnosis of such problems one must consider myelomatosis, hypervitaminosis D, pseudohyperparathyroidism, simple bone cysts, and primary renal disease.
5. The Sulkowitch test offers an instant method of detecting gross hypercalciuria. A presumptive diagnosis depends upon the detection of the characteristic alterations of the serum phosphorus and calcium. Proof of diagnosis depends upon cure of hyperparathyroidism following removal of the adenoma.

The authors wish to acknowledge the careful study and review of the pathologic material by Dr. John Beach Hazard in the cases presented.

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