# HYPERPARATHYROIDISM IN SIBLINGS

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VON RECKLINGHAUSEN first recognized generalized osteitis fibrosa cystica as an entity in 1891, but its etiology was not determined until much later. So many comprehensive reviews of the clinical, metabolic, pathologic and surgical aspects of hyperparathyroidism have appeared in the literature that it is not within the scope of this report to elaborate in detail upon these points. The main features of this disturbance, however, will be illustrated in the case reports of two members of the same family. The bony lesions of these two patients, brother and sister, were first diagnosed erroneously—roentgenologically in one case and pathologically in the other—as giant cell tumors. Later both patients were successfully treated for hyperparathyroidism associated with generalized osteitis fibrosa cystica, by the surgical removal of parathyroid adenomata. Though this disease is not considered to be of a familial nature, these cases illustrate that it may occur in more than one member of the same family and must be differentiated, therefore, from fragilitas ossium and similar familial skeletal disturbances.

## CASE REPORTS

**Case 1.**—An Italian girl, age 17, entered the University of California Hospital January 18, 1934. One year previously she had injured her left shoulder and sustained a pathologic fracture of the neck of the left humerus. She had had no complaints prior to that time. A roentgenologic diagnosis of giant cell tumor was made, the region was immobilized and a course of roentgen therapy instituted. She felt improved for a short time, but later noticed the insidious development of polydipsia, polyuria, constipation, increased fatigability, severe attacks of left ureteral colic, and pain in the left humerus and right tibia. At this time she was seen by Dr. Harold Brunn, who referred her to the University of California Hospital.

Physical examination revealed a girl of short stature, with a waddling gait. She was well developed and her skeletal musculature showed no clinical signs of hypotonicity, although prolonged exertion caused fatigue. Her teeth were in good condition. There was a visible, palpable tumor, apparently located in the left lobe of the thyroid gland. Limitation of motion and swelling of the left shoulder joint were present, as well as tenderness over the left humerus, right tibia, and left kidney.

TABLE I

DAILY AVERAGE EXCRETION OF CALCIUM AND PHOSPHORUS IN CASE 1

| | Case 1. 24-hour Average | | | | | |
|---|---|---|---|---|---|---|
| | Stool | Urine | Total | Intake | Balance | Blood |
| Calcium | 0.1440 | 0.3727 | 0.5167 | 0.929 | −0.4238 | 19.20 mg. per cent |
| Phosphorus | 0.1703 | 0.7027 | 0.8730 | 0.7766 | −0.0964 | 2.56 mg. per cent |
| Phosphatase | | | | | | 33.2 units |

Submitted for publication January 17, 1396.

The serum calcium level was elevated to 19.2 mg., and the plasma phosphatase to 33.2 (Kay-Jenner) units per 100 cc. of blood; the serum phosphorus was lowered to 2.5 mg. A study of the balance of the intake and output of calcium, by Aub's method,[1] revealed a markedly negative calcium balance. On a daily intake of 0.929 Gm. of calcium, the loss was 0.5167 Gm., or a negative balance of 0.4238 Gm. in 24 hours, 75 per cent of which was excreted in the urine (Table I). The urine was cloudy, yellow, acid

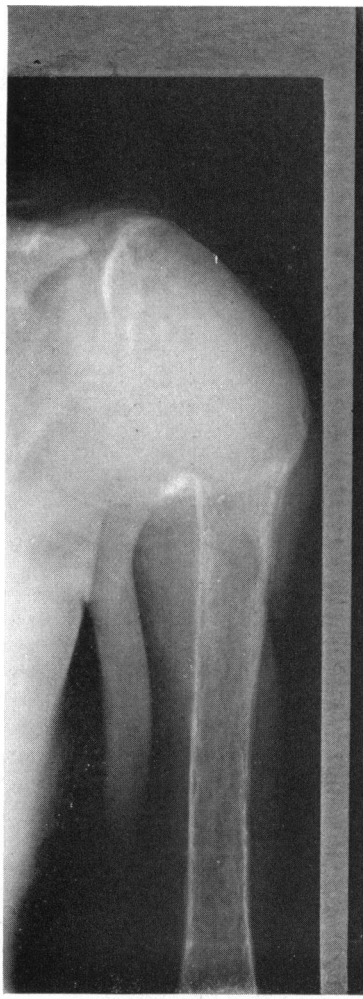

FIG. 1.—Roentgenogram showing marked thinning of the cortex and demineralization of the humerus; there is a cyst of the humeral head.

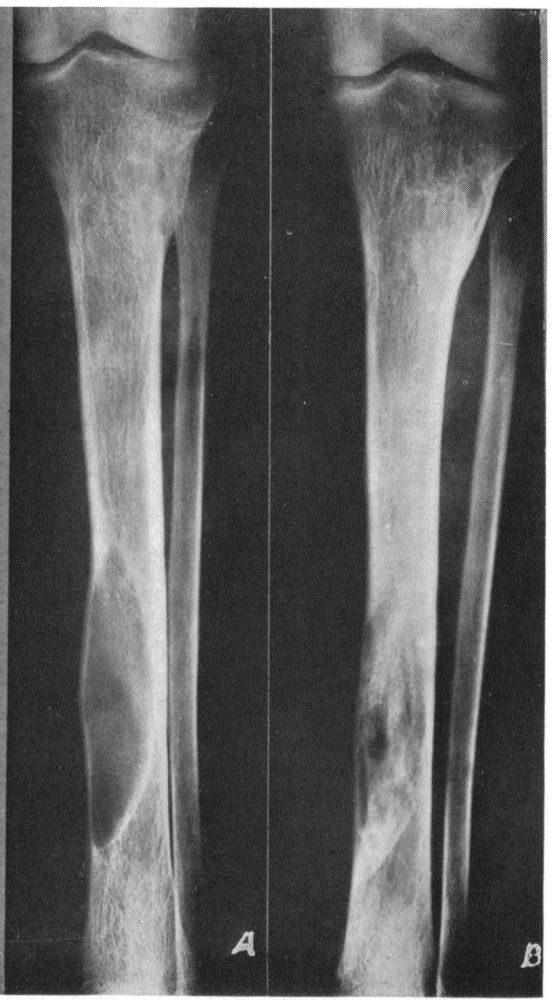


FIG. 2.—Roentgenograms of the right tibia showing a large cyst. (A) Before operation. (B) Thirteen months after the removal of the parathyroid adenoma.

in reaction, and had a specific gravity of 1.022. The test for sugar was negative and there was the faintest possible trace of albumin. From 20 to 25 red blood cells per high dry field were found in the uncentrifuged specimen. The intramuscular phenolsulphonephthalein test showed an excretion of 55 per cent of the dye after two hours. Examination of the blood showed a hemoglobin of 80 per cent, red blood cells 4,230,000, white blood cells 7,870, with 75 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 8 per cent large lymphocytes, 13 per cent small lymphocytes, and 3 per cent monocytes.

The bleeding time was 1.5 minutes (Duke) and the clotting time was five minutes (Lee and White). The tests of blood chemistry showed a fasting blood sugar level of 103.4 mg., non-protein nitrogen 52.1 mg., cholesterol 217.9 mg., serum albumin 4.69 Gm., serum globulin 2.19 Gm., and total protein 6.83 Gm. per 100 cc. of blood. The blood Wassermann and Kahn tests were negative. The basal metabolic rate was plus 1. Serial electrocardiograms showed a shortened Q-T interval (electric systole), delayed auriculo-ventricular conduction and slurred ventricular complexes, indicating hypotonicity of the cardiac musculature.[2]

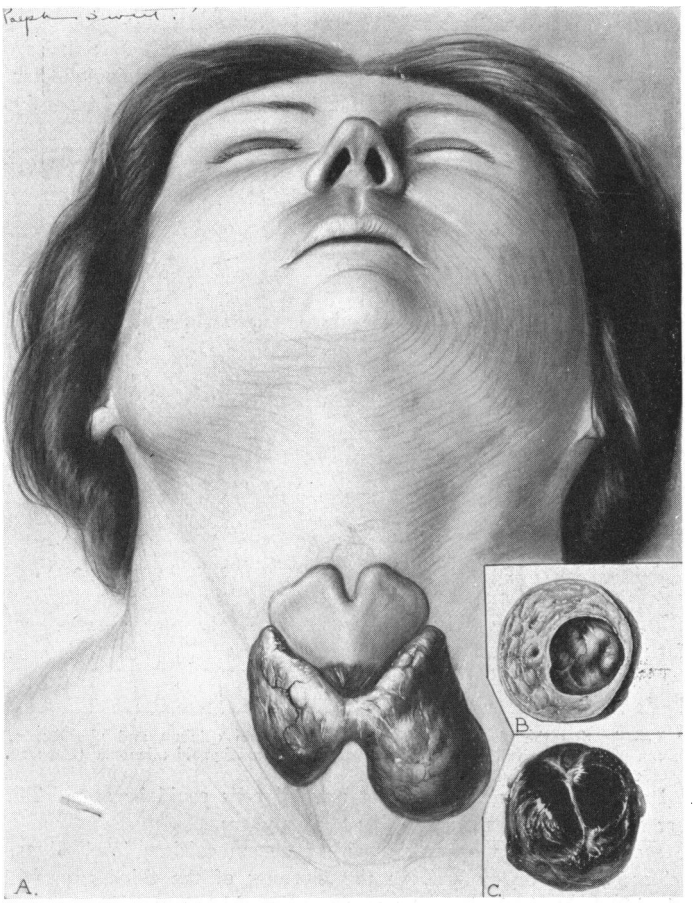


FIG. 3.—(A) Parathyroid adenoma within the capsule of the left lobe of the thyroid gland. (B) Cut section of the adenoma, showing cystic degeneration. (C) Gross appearance of the adenoma after enucleation (Case 1).

Roentgenograms revealed generalized demineralization of the entire skeleton, characterized by uniform granular osteoporosis. Cysts of varying sizes, some with cortical expansion, were present in the humeri (Fig. 1), right tibia (Fig. 2), metacarpal and pubic bones. The trabeculae of the long bones were indistinct and the cortex was thinned. Granular mottling was noted in the skull. The renal shadows were denser than normal and several small calculi were present in the left kidney. Gastro-intestinal roentgenologic series revealed a 40 per cent retention of barium in the stomach after six hours, suggesting hypotonicity of the gastro-intestinal musculature.

After exploring the retrotracheal and retro-esophageal planes of the neck, as well as

palpating the anterior and posterior mediastinum, a parathyroid adenoma, weighing 11.8 Gm. and measuring 3.7 by 2.8 by 3 cm., was removed from within the capsule of the left lobe of the thyroid gland at its inferior pole (Fig. 3). The right lobe appeared to be normal. A normal right inferior parathyroid gland was seen attached to the posterior capsule. The adenoma was inclosed in a smooth capsule, and the cut section revealed a characteristic yellowish-brown surface with a cystic center. The tissue was soft and glistening. The capsule was partially surrounded by a thin rim of normal parathyroid tissue. Microscopic sections showed the tissue to be composed of diffuse sheets or columns of epithelial cells, the majority of which were large, with eccentrically placed hyperchromatic nuclei and abundant clear cytoplasm, conforming to the *wasserhelle* or water-clear type of cell as described by Mallory and Castleman.[6] Some areas showed a pattern with a basal arrangement of the nuclei suggesting a pseudoglandular formation. There were also many groups of typical chief cells of smaller size, and transitional *wasser-*

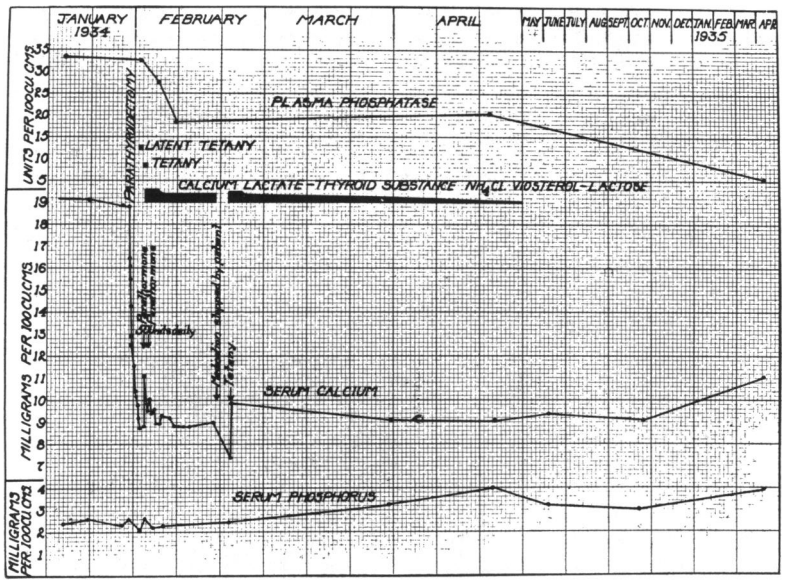


CHART I.—Showing the changes in the levels of serum calcium and phosphorus, and plasma phosphatase following the removal of the parathyroid adenoma (Case 1).

*helle* cells. Rarely a small group of light oxyphil cells could be seen. These cellular elements were supported by a stroma of fine fibrous tissue.

On the second day after operation, with a serum calcium level of 10.2 mg., the patient developed latent tetany and, on the morning of the third day, with a serum calcium level of 8.8 mg., she had spontaneous parathyroid tetany (Chart 1), characterized by carpopedal spasms, numbness, and paresthesias. Treatment with parathormone, calcium lactate, thyroid substance, ammonium chloride, lactose, and viosterol brought the calcium and phosphorus in the blood to a normal level. The pain and tenderness in the bones disappeared within three days after operation. The patient developed a positive calcium balance, with normal levels of calcium, phosphorus, and phosphatase in the blood; she no longer had pain and tenderness in the bones, hematuria or ureteral colic. Roentgenologically the skeleton showed increased calcification or complete obliteration of the cysts, 13 months after the removal of the parathyroid adenoma. The electrocardiogram revealed that the shortened Q-T interval had become prolonged and the other abnormal findings had reverted toward the normal. There was no retention of barium in the stomach after six hours. Both of these findings suggest a change from a state of muscu-

lar hypotonicity toward normal. At the last examination, she had no symptoms except some limitation of motion of the left shoulder joint resulting from the cystic formation and pathologic fracture.

**Case 2.**—After the first patient was studied, it was discovered that her brother, age 23, was being treated for a giant cell tumor of the mandible. At this time eight other members of the family were examined, but no clinical or metabolic evidence of skeletal or renal disease was found. Seven months before we saw this second patient, he had noted a painful swelling of the symphysis of the mandible and later sustained a pathologic fracture. A biopsy revealed a giant cell reaction which was interpreted as being indicative of a giant cell tumor. The patient was given a course of roentgen therapy, without improvement. He then developed general malaise and easy fatigability but had no pains in other parts of his skeleton and no urinary symptoms. Because of his sister's improvement, he came to the hospital for further investigation.

Physical examination revealed a well developed man of short stature, with a tender swelling of the mandible and a small palpable nodule in the left lobe of the thyroid gland. His teeth were sound. There was no clinical evidence of hypotonicity of his skeletal musculature or tenderness over his bones. The remainder of his examination was negative.

The serum calcium was elevated to 17.5 mg., the plasma phosphatase to 10.3 units (Kay-Jenner) per 100 cc. of blood, and the serum phosphorus was lowered to 1.5 mg. There was a markedly negative calcium balance. On a daily intake of 0.1040 Gm. of calcium, the loss was 0.3782 Gm., or a negative balance of 0.2742 Gm. in 24 hours, 80 per cent of the excretion being in the urine (Table II). Urinalysis revealed clear, yellow,

TABLE II

DAILY AVERAGE EXCRETION OF CALCIUM AND PHOSPHORUS IN CASE 2

| | Case 2. 24-hour Average | | | | | |
|---|---|---|---|---|---|---|
| | Stool | Urine | Total | Intake | Balance | Blood |
| Calcium | 0.0480 | 0.4302 | 0.4782 | 0.1040 | −0.3742 | 18.20 mg. per cent |
| Phosphorus | 0.2801 | 0.7676 | 1.0477 | 0.8480 | −0.1997 | 2.10 mg. per cent |
| Phosphatase | | | | | | 10.3 units |

neutral urine, without albumin or sugar. The centrifuged specimen showed a rare hyaline cast and 10 pus cells per high dry field. No red blood cells were found. Examination of the blood showed the hemoglobin to be 90 per cent, red blood cells 4,300,000 and white blood cells 4,150, with 60 per cent polymorphonuclear neutrophils, 26 per cent lymphocytes, 4 per cent eosinophils, and 14 per cent monocytes. The blood sugar estimation was .068 mg., and the non-protein nitrogen was 30.6 mg. per 100 cc. of blood. The blood Wassermann and Kahn tests showed a four plus reaction. The basal metabolic rate was minus 23. The kidneys excreted 35 per cent of the phenolsulphonephthalein after two hours. The Q-T interval of the electrocardiogram was shortened.

Roentgenograms revealed generalized changes characteristic of primary hyperparathyroidism. A generalized demineralization of the skeleton was noticeable, with findings similar to those in Case 1. This patient had only one cyst of the symphysis of the mandible (Fig. 4) and a small cyst in one of the phalanges. There were no renal calculi present. Roentgenograms of the esophagus showed a notched deviation to the right just below the level of the larynx (Fig. 5). Otherwise the gastro-intestinal series was negative.

An adenoma of the left inferior parathyroid gland, weighing 6.5 Gm. and measuring 3 by 2 by 2 cm., was removed from a retrotracheal position on the same plane as the esophagus (Fig. 6). The palpable nodule in the left lobe proved to be a small adenoma of the thyroid gland. The gross appearance of the parathyroid adenoma was charac-

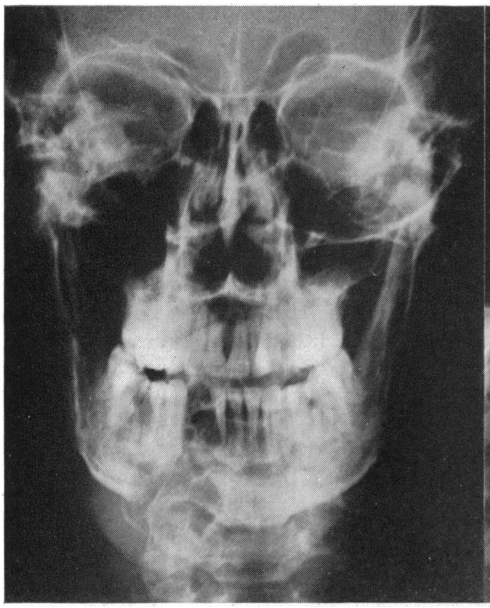

FIG. 4.—Roentgenogram showing a cyst of the mandible with a pathologic fracture (Case 2).

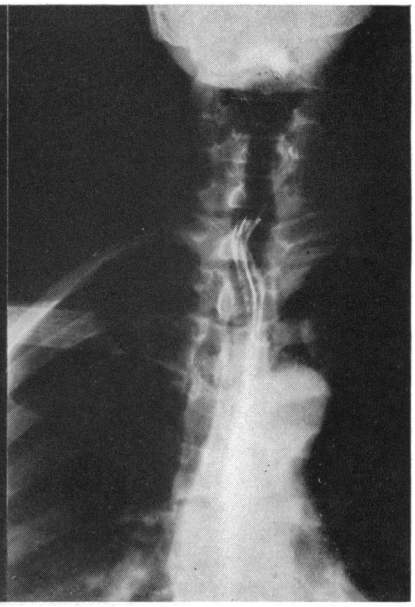

FIG. 5.—Roentgenogram showing the deflection of the esophagus by a retrotracheal parathyroid adenoma (Case 2).

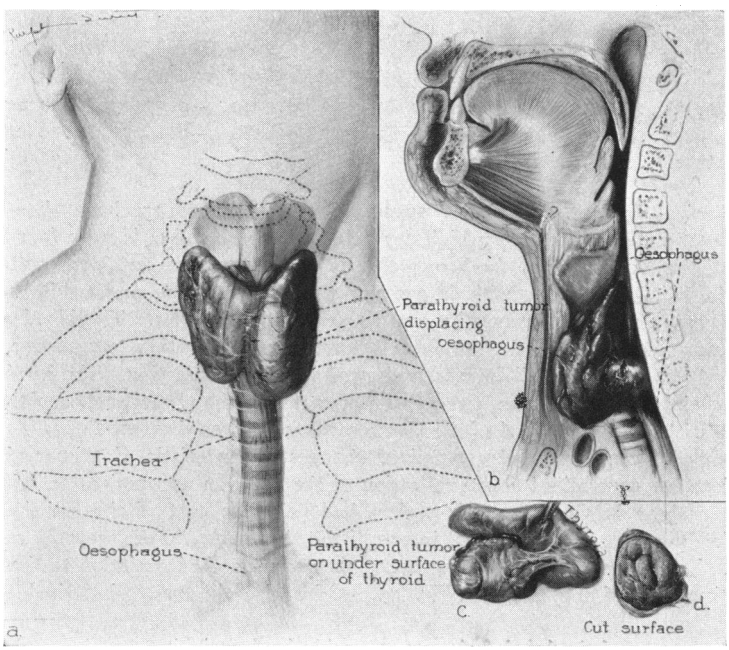


FIG. 6.—The position of the parathyroid adenoma in Case 2; (a) Anteroposterior view, showing the deflection of the esophagus to the right. (b) Left lateral view demonstrating the retrotracheal position of the adenoma. (c) Comparative sizes of the adenoma and the left lobe of the thyroid gland. (d) Cut surface of the adenoma.

teristic and it had a thin rim of compressed normal parathyroid tissue on its border. Microscopically, it was composed mainly of chief cells with numerous large groups of pale oxyphil cells. No *wasserhelle* cells were seen.

No signs of tetany developed, and the blood chemistry returned to normal (Table III and Chart 2). Fourteen months after operation, the patient was entirely free from

TABLE III

DAILY AVERAGE EXCRETION OF CALCIUM AND PHOSPHORUS IN CASE 2

HIGH CALCIUM, LOW PHOSPHORUS DIET
POSTOPERATIVE STUDIES

First period 4 days, 24-hour Average

| | Stool | Urine | Total | Intake | Balance | Blood |
|---|---|---|---|---|---|---|
| Calcium*..... | 0.5960 | 0.1922 | 0.7882 | 0.8570 | +0.0688 | 16.99 to 9.34 mg. per cent |
| Phosphorus..... | 0.1790 | 0.0643 | 0.2433 | 0.7160 | +0.4727 | 1.93 to 2.74 mg. per cent |

Second period 3 days, 24-hour Average

| | | | | | | |
|---|---|---|---|---|---|---|
| Calcium†..... | 0.6933 | 0.0265 | 0.7198 | 1.5823 | +0.8625 | 9.70 mg. per cent |
| Phosphorus..... | 0.1433 | 0.3307 | 0.4740 | 1.2940 | +0.8200 | 2.44 mg. per cent |

* The first postoperative study was from March 19 to March 22, inclusive. There was no intake on March 19—the day of operation. No calcium was given other than in the diet. Aspirin and codeine were the only drugs administered.

† The second postoperative study was from March 23 to March 25, inclusive. No calcium was given other than that in the diet. Phenobarbital was the only drug administered.

symptoms, the cyst of the mandible was becoming calcified and smaller, and calcification of the demineralized skeleton was taking place. The shortened Q-T interval of the electrocardiogram became prolonged and his renal function improved. Fatigue, which

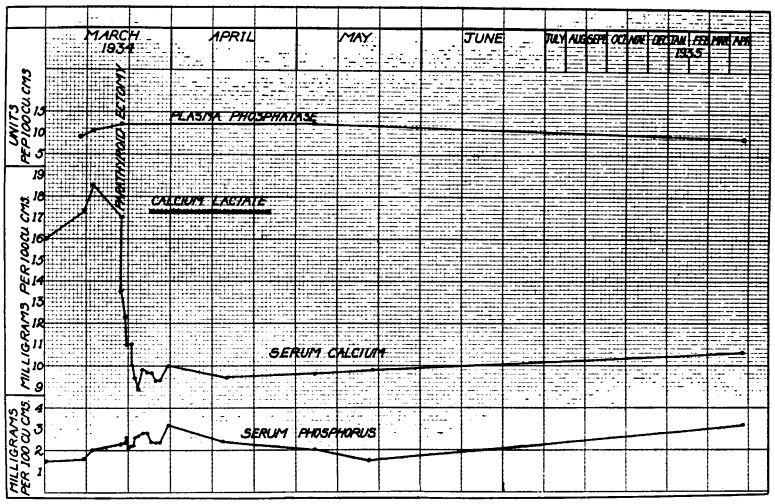


CHART 2.—Showing the changes in the levels of serum calcium and phosphorus, and plasma phosphatase following the removal of the parathyroid adenoma (Case 2).

had been an outstanding symptom, disappeared completely and the patient was able to perform manual labor.

COMMENT.—These two case reports illustrate the clinical, metabolic, and roentgenologic findings associated with the classic type of von Recklinghausen's disease. The levels of calcium and phosphorus in the blood were striking (Tables I and II). In both cases there was evident hypercalcemia. Conversely, the phosphorus was lower than normal. In the first case, the phosphatase was definitely elevated. In the second, it was not so obviously so, and we are inclined to correlate this with the lessened involvement of bone, inasmuch as the amount of phosphatase is an index of the activity of bony metabolism (destruction and repair).

One patient had renal calculi; the other did not. On the basis of the metabolism, one could not anticipate which patient would have kidney stones, since, in both instances, the excessive urinary loss of calcium and phosphorus would presumably favor the formation of such stones. Perhaps the extent of the process in the first patient would suggest a disturbance of metabolism of longer standing, which would favor lithiasis.

The postoperative studies in the second case are interesting (Table III), as we may observe the transition from the hypercalcemia of hyperparathyroidism to the hypocalcemia of hypoparathyroidism. Obviously, however, the tests were not comparable to those made before operation, since the intake of calcium was many times greater (for the 24 hour period) than in the preoperative test, so that there was a disproportion between the intake of calcium and that of phosphorus.

As Shelling and Goodman[3] have shown, it is important to meet the immediate reversal of function following parathyroidectomy by a diet low in phosphorus and high in calcium, which helps to guard against further depression of the calcium. While this is ordinarily accomplished by administration of calcium, we believe that a careful restriction of phosphorus is of additional benefit. Additional calcium was not given in the cases cited, as we desired a minimal intake in order to detect the endogenous (endocrine) factors.

This study illustrates remarkably well the shift of the excretion of calcium from urine to stool, and the change to a positive balance. That this is a temporary phenomenon must be admitted, since follow up subsequently has shown no persistent tetany and no hypocalcemia. We think it likely that a further study might show a readjustment to that of the normal adult metabolism.

In each of these two cases, an erroneous diagnosis of giant cell tumor was made, roentgenologically in one, and microscopically, after biopsy, in the other. There are certain differentiating points between giant cell tumor and the giant cell variant of osteitis fibrosa cystica. The former is usually situated asymmetrically at the epiphyses of the long bones; namely, the lower end of the radius and femur and the upper end of the tibia, and usually is single rather than multiple. The giant cell variant of osteitis fibrosa may occur in the shaft of the bone, subperiosteally or centrally, and is associated with generalized demineralization of the skeleton and altered calcium and phos-

phorus metabolism. This lesion is more likely to be multiple. Although there is some controversy concerning this differentiation by pathologic means, many contend that there is a difference in the stroma. If one includes a small portion of surrounding bone proper, in the biopsy, the histologic picture of osteitis fibrosa should be evident enough to suggest hyperparathyroidism in those cases of giant cell variant.

Both patients sought medical attention because of pathologic fractures. The patient with the more advanced demineralization of the skeleton, longer history, higher serum calcium level, and larger tumor, developed tetany after operation, while the other patient, having these characteristic findings in a lesser degree, did not develop signs of hypoparathyroidism. The first patient developed symptoms and signs of latent tetany on the second day after operation with a normal serum calcium level of 10.2 mg., indicating that a sudden drop in the amount of calcium in the serum may produce symptoms suggesting hypocalcemia in the same way that the sudden drop in blood sugar level may produce symptoms suggesting hypoglycemia in a patient with diabetes mellitus, even though the actual level is normal or above.

In each case, the symptoms and signs rapidly disappeared following the removal of the parathyroid tumors, and a deposition of minerals in the skeleton took place within a short time. A markedly negative calcium balance became positive after parathyroidectomy, indicating that reconstruction of the skeleton was taking place. In time, a normal negative balance may be expected to supersede this. The outstanding symptoms of easy fatigability underwent the most marked subjective improvement.

DISCUSSION.—There are three important types of parathyroid hyperfunction (exclusive of that caused by malignant tumors): the adenomatous, the hyperplastic associated with renal calculus, and the secondary, compensatory hyperplastic type. Only in the first two is parathyroidectomy indicated.

In 1907, Erdheim,[4] by experimental and anatomic means, demonstrated the enlargement of all the parathyroid glands in osteomalacia. He concluded that this enlargement was of a secondary, compensatory nature—that is, a result, rather than a cause, of disease of the skeleton. It was found later that this secondary parathyroid hyperfunction was associated with other types of diseases of the skeleton, such as arthritis, osteitis deformans, multiple myeloma, metastatic carcinoma and rickets, as well as scleroderma and nephritis. We had the opportunity to study a young patient with renal rickets who, at autopsy, showed the same type of hyperplasia of all the parathyroid glands.[5]

In the consideration of hyperparathyroidism associated with generalized osteitis fibrosa cystica, a careful distinction must be made between this secondary, compensatory parathyroid hyperplasia and parathyroid adenoma. Parathyroid enlargement, with resulting hyperparathyroidism, may be either hyperplastic or adenomatous. Hyperplasia affects all the tissue, but an adenoma usually involves only one, or at most two, of the glands. It seems logical to assume that hyperplasia, therefore, is dependent upon an external

stimulant while an adenoma is the result of local factors caused by neoplastic growth.[6]

In 1925, Mandl[7] removed a large parathyroid adenoma from a patient who thereafter obtained marked clinical improvement in the skeletal symptoms and signs of generalized osteitis fibrosa cystica. Following the report of this operation, parathyroidectomy was performed for many of the previously named conditions, until it was established that generalized osteitis fibrosa cystica is the only one of these diseases caused by a parathyroid adenoma. Microscopically, Mallory and Castleman[6] differentiated hyperplasia from adenomatous enlargement. They found the chief cell, or one of its transition, to be the important constituent of the adenoma associated with hyperparathyroidism in the majority of cases.

Recently Albright[8] discovered several cases of hyperplasia of the parathyroid glands by obtaining routine serum calcium and phosphorus determinations on patients with renal calculi. Those patients who showed a high serum calcium and a low serum phosphorus, though they showed no skeletal changes or elevation of the plasma phosphatase, were operated upon and enlarged hyperplastic parathyroid glands of different sizes removed. These patients improved following the removal of the main bulk of their parathyroid tissue. They seem to fall into a separate group from the secondary hyperplasias mentioned above. We have not encountered such a case nor any reports of similar cases from other clinics.

One should be familiar not only with the anatomic regions encountered in the ordinary thyroidectomy but also with the appearance, aberrant locations, and difficulties in locating tumors of the parathyroid glands. Roentgenologic evidence of deviation of the trachea or esophagus may aid in locating the tumor before operation. Walton,[9] Churchill,[10] and Lahey[11] have emphasized the importance of being prepared to make a thorough search in the retrotracheal and retro-esophageal planes of the neck, the lateral triangles of the neck, and in the anterior and posterior mediastinum. To overlook the tumor at the first operation may rob the patient of a chance for cure, because of the great difficulty in exploring the neck and mediastinum subsequently through a firm bed of scar tissue. We feel that, if a tumor is not found, removal of a normal parathyroid gland is not only without therapeutic effect but may be harmful. Likewise, we are skeptical concerning the removal of normal glands for many conditions alleged to result from parathyroid hyperfunction.

## CONCLUSIONS

(1) Primary hyperparathyroidism is a clinical entity caused by one or more parathyroid adenomata and has a definite train of clinical, metabolic and roentgenologic findings. The diagnosis is based on a study of these three factors and not on any one alone. Primary hyperparathyroidism should not be confused with secondary compensatory parathyroid hyperplasia.

(2) The two cases reported show that the presence of malacic disease

in two members of the same family does not necessarily point to a diagnosis of fragilitas ossium or to any other type of familial skeletal disturbance.

(3) When a diagnosis of giant cell tumor is made by pathologic or roentgenologic methods, metabolic studies should follow.

(4) A conservative attitude should be taken concerning the removal of normal or hyperplastic parathyroid glands for a multiplicity of conditions.

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