HYPERPARATHYROIDISM

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Since the discovery of the parathyroid glands by Sandström, in 1880, an occasional case of parathyroid hypertrophy or tumor has been reported in patients with osteomalacia, osteitis fibrosa, paralysis agitans, rickets, tetany, chronic nephritis, and epilepsy. DaCosta, in 1909, could find only seven cases reported in the literature. He added one more. In five of these the condition was found incidentally at necropsy; three were operative cases but did not present pathognomonic features. Hoffheinz, in 1925, reviewed pathologic reports of forty-five cases of enlarged parathyroid glands. In twenty-seven of these, there was disease of the skeleton (osteitis fibrosa, seventeen; osteomalacia, eight; and rickets, two). Lloyd, in a recent review of 10,000 consecutive necropsies, found five parathyroid tumors. As early as 1903, Erdheim commented on the frequency of the occurrence of the combination of the foregoing diseases of bone and parathyroid tumors. He advanced the hypothesis that the parathyroid enlargement might be an inadequate attempt at compensatory organic hypertrophy effected by the pathologically disturbed calcium metabolism. On the basis of this, Mandl, in 1925, transplanted healthy parathyroid glands into a patient with generalized osteitis fibrosa, but this had no effect on the progressive course of the disease. He then explored the region of the parathyroid glands and removed a parathyroid adenoma. Following this, the patient spectacularly improved. This led Mandl to conclude that in some cases, at least, the parathyroid tumor is primary and the bony changes are secondary. Nine cases have been reported with some or all of the features of the syndrome which Barr, Bulger, and Dixon called hyperparathyroidism. In five of the nine cases, operation was performed and tumors were removed. In one case of the nine, two apparently normal, but undoubtedly hyperfunctioning, parathyroid glands were removed. Three patients were not operated on and there is no proof of the presence of tumors, but many of the clinical features were present.

The clinical features to be noted in general are (1) high concentration of serum calcium; (2) low concentration of serum phosphorus; (3) abnormal excretion of calcium in the urine; (4) rarefaction of bones; (5) occurrence of multiple cysts or tumors of bones; and (6) hypotonia and muscular weakness. A negative calcium balance might properly be included, since in every case in which studies of excretion of calcium and phosphorus were done, a negative calcium balance was found, except in the case of Wilder's patient. In this instance the determinations were done several days after the institu-

tion of a high-vitamine diet and daily exposures to ultraviolet light. This the author considered to be the cause of the slightly positive calcium balance found at that time. Following the removal of the parathyroid tumor these studies were repeated and huge amounts of calcium were found to be retained.

In the five cases of parathyroid tumor and the one case of hyperfunctioning parathyroid glands, the sexes were equally divided and the ages ranged from twenty-eight to fifty-six years, as far as is known. The age of the patient in the case reported by DuBois, Aub, Bauer, and Richardson's patient is not known. All the patients were weak, tired, and were either unable to walk or found difficulty in walking. All but one had pain. The pain was prone to affect the extremities. If the patients could assume the upright position, the posture was poor. Kyphosis, dorsum rotundum, and bow legs were to be seen in various cases. Polydipsia and polyuria seemed to have some significance, although they were not constant symptoms. At some time during the course of the disease, frequently early, attacks of nausea, vomiting, and abdominal pain, associated at times with marked constipation, were to be noted. This was especially evident in the cases reported by Gold and by Boyd, Milgram, and Stearns. These attacks disappeared promptly on removal of the parathyroid tumor. Muscular weakness, hypotonia, and lassitude were noted in a number of cases, especially in the cases reported by Mandl, by DuBois, Aub, Bauer and Richardson, and by Barr, Bulger and Dixon. Rarefaction of bones was present in every proved case and in all but one of the unproved cases. This was always so marked as to be called osteitis fibrosa cystica on the basis of the röntgenograms. Fractures of these rarefied bones were reported in half of the cases. Multiple cysts or tumors of the bone were frequently encountered. Loss of weight was usually marked, and, in some cases, extreme.

In each of the five cases in which a parathyroid tumor was removed and in the one case in which hyperfunctioning parathyroid glands were removed, there was striking improvement in the clinical picture after the first few days. Usually, immediately after the tumor is removed, these patients show evidence of tetany. Immediately after operation the high concentration of serum calcium dropped to far below normal, and it was usually weeks before it gradually rose to within normal limits. In those cases in which metabolic studies of calcium and phosphorus were done after removal of the parathyroid tumors there was marked retention of both. In the case reported by Boyd, Milgram, and Stearns, there was a remarkably rapid and complete return to normal of the urinary symptoms and signs soon after the operation. The tumors removed in four of the cases were adenomas, and in one case the tumor was malignant. Wellbrock, in 1929, renewed the subject of malignant adenoma of the parathyroid glands.

Duken reported two of the three cases in which operation was not done. Both patients presented some of the features of hyperparathyroidism.

One patient died of generalized sarcomatosis some time after the original

report of the case was printed, and in the other case an operation was not done, so neither of these cases can be accepted as proved. Box and DeWesselow, in 1925, reported a case of "chronic nephritis with possible parathyroid syndrome." This case presented many of the features of hyperparathyroidism but the suspicion that a parathyroid tumor was present was not confirmed by operation or necropsy.

The case reported herewith is the seventh proved case of hyperparathyroidism and the sixth in which this condition was due to tumor. These cases record a remarkably complete and relatively new clinical syndrome. Based on knowledge of the physiology of the parathyroid glands, as recently demonstrated by Collip, by Greenwald and Gross, by Albright and Ellsworth, and by others, these cases represent exactly what one would expect if the body were subjected to an excess of the parathyroid secretion over a relatively long time. Albright and Ellsworth recently made complete studies on a young Italian boy whose condition they had diagnosed as hypoparathyroidism. The criteria on which this diagnosis was made were (1) low serum calcium; (2) high serum phosphorus; (3) cataract; (4) normal density of bones; and (5) aggravation of tetany by exertion. All of the cases referred to in this report demonstrate exactly converse changes.

REPORT OF CASE.—A girl, aged fourteen years, registered at The Mayo Clinic November 23, 1929. The chief complaint was of spells of vomiting, pallor, and loss of weight. She had always been healthy and robust until about sixteen months previously. In July, 1928, she had begun to be a little pale, to lose weight, and to be generally below normal physically. Her weight had decreased from eighty-six to fifty-five pounds from the onset of her trouble to the date of admission. Beginning in the summer of 1928 she had become constipated and had required cathartics until two months before her admission, when movements of her bowels had become, and had remained, fairly regular. October 4, 1928, she had had her first spell of vomiting. This had lasted twenty-four hours. During this period she had been unable to retain anything in her stomach. After that time, the spells had recurred at intervals of never more than two weeks and had lasted from one to five days. These attacks had seemed to appear without cause. Food did not act as a predisposing cause. Between attacks she could eat anything with impunity. The last attack had begun one week before her registration at the clinic and had continued five days. She had had polydipsia and polyuria, with consequent

TABLE I

Variations in blood serum calcium and phosphorus

Date, 1929	Calcium milligram in each 100 cubic centimetre	Phosphorus milligram in each 100 cubic centimetre
November 4	16.32	2.46
November 5	17.67	2.80
November 15	15.50	3.2
November 16	Operation	
November 18	7.89	2.2
November 25	7.74	3.41
November 29	7.56	3.9
December 5	7.85	4.04
December 12	10.36	3.57

nocturia three to five times each night for the preceding year. She consistently drank about two quarts of water each night.

The patient weighed fifty-five pounds, whereas the standard weight for her height and age was ninety pounds. She was pale, emaciated, and appeared to be chronically ill. Electrical irritability was decreased. Otherwise, the general examination gave essentially negative results.

Complete gastro-intestinal studies did not reveal organic lesions. The blood count revealed moderate secondary anæmia. Urine varied in amount from 750 to 3150 cubic centimetres; specific gravity, on daily examination varied from 1.004 to 1.010. The urine usually contained a trace or a faint trace of albumin and occasionally a few pus cells. Excretion of phenolsulphonephthalein on one occasion was 40 per cent. and on another 45 per cent. in two hours. The concentration of blood urea on the day of admission was 80 milligrams in each 100 cubic centimetres. The following day it was 37 milligrams in each 100 cubic centimetres and it never thereafter rose above 40 milligrams. In Table I are given the variations in the concentration of serum calcium and serum phosphorus during her stay at the clinic. Röntgenograms of all the bones gave evidence only of diffuse decalcification, without loss of normal structure of the bone (Figs. 1, 2 and 3). Repeated tests of water concentration were done, all of which disclosed definite fixation of specific gravity. Polydipsia or polyuria were not constant while the patient was under our observation. A study, for three days, of calcium and phosphorus in the urine and the stool revealed a slightly positive phosphorus balance and a slightly negative calcium balance.

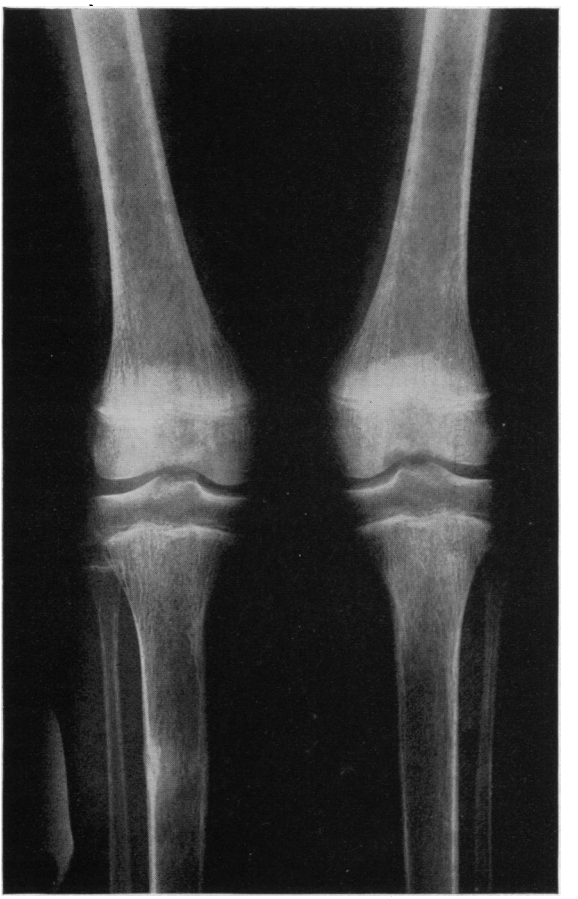

FIG. 1.—Generalized rarefaction of femurs and tibias.

In view of the similarity of this case to several of the other cases of hyperparathyroidism, a tentative diagnosis of parathyroid tumor was made, although careful palpation of the neck with this in mind did not reveal tumor in the parathyroid region.

November 16, 1929, operation was performed. The thyroid gland was found to be about normal in size, but it contained a little more colloid material than normal. Lying behind the left lobe of the thyroid gland at the inferior pole and outside of the capsule but attached thereto, was a tumor which measured 1.5, 1.25 and 1.25 centimetres in various diameters (Fig. 4). It was definitely brownish and the contrast in color between the tumor and remainder of the thyroid gland was marked. The color and situation of

the tumor indicated it to be an adenoma of the left inferior parathyroid body. The tumor was removed. Other parathyroid bodies could not be seen. The right lobe of the thyroid gland was elevated also and there was no tumor behind this. Nothing was done

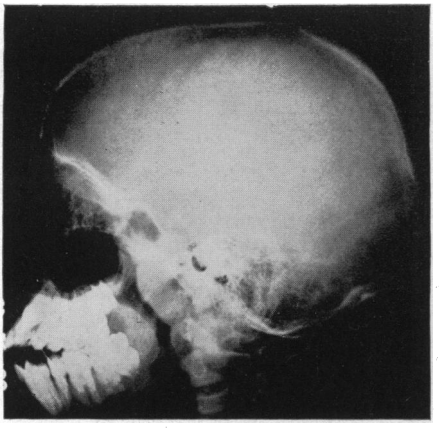

FIG. 2.—Generalized rarefaction of skull.

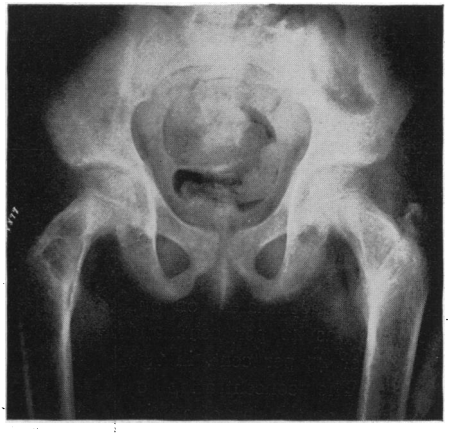

FIG. 3.—Generalized rarefaction of pelvis.

to the thyroid gland. Pathologic study of the tissue removed (Fig. 5) disclosed that it was a parathyroid tumor (adenoma) weighing 16 grains (1 milligram).

The effect of the operation was remarkable. The following day the patient complained of numbness and tingling in the fingers and toes, and Chvostek's sign was present

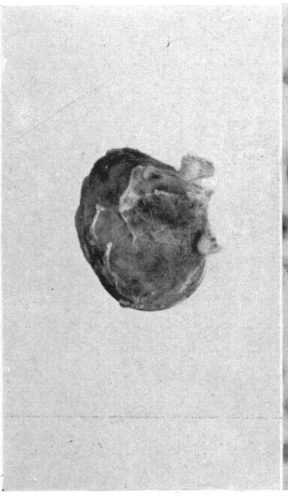

FIG. 4.—Gross specimen of parathyroid adenoma. Dimensions 1.5, 1.25 and 1.25 centimetres in various diameters.

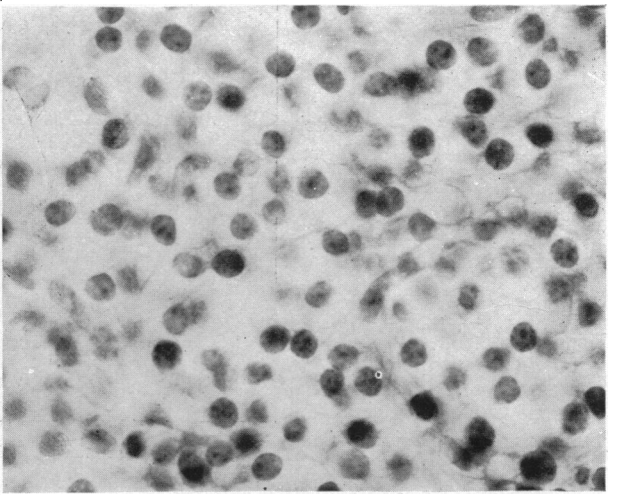

FIG. 5.—Structure of parathyroid adenoma (x 750).

at irregular intervals for several days. The tingling and numbness became worse, and November 19, 5 cubic centimetres of solution of calcium chloride, 10 per cent., administered intravenously, gave relief even before the injection was completed. Later the same day the sensation returned to a lesser degree and was relieved by 10 units of parathyroid extract-Collip (para-thor-mone) given subcutaneously. Beginning a few hours after the

operation, cod-liver oil, viosterol, and calcium chloride were administered daily. The second day after operation the concentration of serum calcium was 7.89 milligrams and

TABLE II

Studies of metabolism of calcium and phosphorus†*

	Three days pre-operative, average, gram		Three days post-operative, average, gram	
	Calcium	Phosphorus	Calcium	Phosphorus
Intake	5.36	4.62	4.485	3.85
Output				
Urine	1.474	2.38	0.03	0.725
Stool	4.10	1.36	2.03	0.740
Total	5.57	3.74	2.06	1.46
Balance	—0.21	+0.88	+2.42	+2.39

* Determinations of inorganic calcium were done according to the method of Kramer and Tisdall except that acidity was adjusted to pH 4.8 to 5.2, the indeterminate range of methyl red; this is according to Shohl.

† Determinations of phosphorus were done according to the method of Fiske and Subbarow.

of phosphorus 2.2 milligrams in each 100 cubic centimetres. It was not until December 12 that the concentration of serum calcium and phosphorus returned to normal limits (Table I). Studies of metabolism a few days after operation revealed a markedly positive calcium balance (Table II). Electrical excitability of the nerves approached normal (Table III). After operation the amount of urine remained practically the same as before operation. Excretion of phenolsulphonephthalein was again 45 per cent.

TABLE III

Contraction caused by electrical stimulation of ulnar nerve

	Milliamperes				
Date, 1929	Kathodal closing	Anodal closing	Anodal opening	Kathodol opening	Kathodol closing tetanus
November 13	1.8	2.8	4.8	5.2	5.8
December 11	1.2	2.2	3.8	5.6	6.4

The water concentration tests before operation revealed a striking loss of ability to concentrate fluids (Table IV). In none of the tests done before operation did the specific gravity rise above 1.015 and in none of the tests done within four weeks after the operation did the specific gravity reach 1.017. Polydipsia and polyuria were less marked after operation, although this had seemed to occur with some irregularity previously. It was

TABLE IV

Water concentration tests

Date, 1929	Time	Amount, cubic centimetre	Specific gravity
November 1	11 a.m.	95	1.011
	2 p.m.	70	1.014
	5 p.m.	70	1.015
	8 p.m.	75	1.013
	8 a.m.	300	1.011
November 4	11 a.m.	225	1.009
	2 p.m.	200	1.010
	5 p.m.	175	1.010
	8 a.m.	200	1.010

Date, 1929	Time	Amount cubic centimetre	Specific gravity
November 9	11 a.m.	150	1.010
	2 p.m.	100	1.011
	5 p.m.	50	1.010
	8 p.m.	125	1.010
November 16	Operation		
December 6			
	5 p.m.	270	1.012
	8 p.m.	75	1.015
	8 a.m.	450	1.015
December 12	11 a.m.	75	1.016
	2 p.m.	140	1.014
	5 p.m.	175	1.015
	8 p.m.	100	1.015
	8 a.m.	450	1.013

never as marked while the patient was in the hospital as before admission. Appetite was noticeably improved and there were no more vomiting spells. Röntgenograms of the bones taken after operation did not give evidence of increase in density.

Comment.—Albright and Ellsworth, on the basis of their work and of that of Albright, Bauer, Ropes, and Aub, suggested the following hypothesis of the mode of action of parathyroid extract-Collip (para-thor-mone). This seems a most logical hypothesis to account for the changes in the reported cases of hyperparathyroidism. "When parathormone is administered, the equilibria of the body fluids are upset in such a way that an increased phosphorous excretion is a necessary result. We do not know the cause of the increased phosphorous excretion, but as a result of this increased phosphorous excretion the body fluids become depleted in phorphorus. The falling serum phosphorus is evidence of this. As the phosphorus and consequently the phosphate ions in the serum fall, there is a tendency to an unsaturation of the blood with calcium phosphate. This tendency is met by a mobilization of calcium from the bones. Thus a deficit of phosphate ions is being supplied by calcium and phosphate ions. Consequently the serum calcium rises. With a rise in serum calcium, provided the level is not below the threshold for calcium excretion, there is a rise in urinary calcium output."

When the patient in Albright and Ellsworth's case of hypoparathyroidism was under the influence of parathyroid extract-Collip (para-thor-mone) they noted marked polyuria at night. This fact and the presence of polyuria and more or less fixed specific gravity in many of the cases of hyperparathyroidism leads one to suspect disturbed water balance rather than true renal injury. This view is strengthened by the complete, and, at times, rather rapid, return to normal of renal function after removal of a parathyroid tumor.

The occurrence of osteitis fibrosa, multiple giant-cell tumors, and bone cysts, has been explained by Geschecktér and Copeland. They considered that a cyst of bone is an arrested giant-cell tumor; that its formation is a reparative process; and that if multiple cysts and giant-cell tumors are present, some

complicating factor is present which prevents the giant-cell tumors from forming cysts of bone. They presented cases of osteogenesis imperfecta, rickets, syphilis, fragilitas ossium, and osteomalacia in association with multiple cysts of bone and giant-cell tumors.

The general picture of osteitis fibrosa and, in many cases, the occurrence also of multiple cysts of bone and giant-cell tumors, is exactly what one would expect if one accepts Geschеckter and Copeland's theory as to their formation. The pain and weakness in the extremities are the direct results of the bony and muscular changes, which are themselves accounted for by the excess of parathyroid secretion in the blood-stream. This also explains the high concentration of serum calcium, the low concentration of serum phosphorus, and the negative calcium balance. There is excellent corroboration of this in the experimental work of Collip and others. Certainly the occurrence of hyperparathyroidism, with its train of changes in bone, would be an ideal complicating factor.

There is no adequate explanation for the frequent occurrence of gastro-intestinal symptoms in the group of cases which has been reported in the literature and which were present in the case reported in this paper. In five cases constipation was a prominent symptom, and in the same cases attacks of abdominal pain accompanied by vomiting had been the outstanding feature of the disease at some time during its course. Frequently these were early manifestations and had entirely disappeared before the patient was admitted to hospital.

The same also might be said of the urinary symptoms. In one case the presence of a renal pelvis full of stones, on which was superimposed a pyogenic infection, would satisfactorily explain the symptoms. In none of the other three cases in which these symptoms were marked was there a suitable or even a plausible explanation unless the hypothesis advanced by Albright and Ellsworth is to be accepted. Accepting the disturbance of water metabolism as the cause of the renal dysfunction, when so little is really known about this subject itself, is to open a question over which there has been considerable controversy. However, we can think of no other explanation which would so satisfactorily explain the rapid return to normal of some of the urinary symptoms after the parathyroid tumor was removed.

Our patient is the youngest who has been proved to exemplify the clinical syndrome which is the subject of this paper. The symptoms of this patient were of shorter duration and the chief complaints related to the gastro-intestinal and genito-urinary systems rather than to the osseous system as in all the other cases. Although the röntgenograms of bones did reveal evidence of diffuse decalcification of all the bones, they certainly did not disclose anything that was characteristic for osteitis fibrosa. We have no means of knowing to what extent the process in the bones would have gone had the parathyroid tumor not been removed. Probably the patient would have had symptoms referable to the osseous system had the negative calcium balance persisted for a sufficiently long time. Following operation the gastro-intes-

tinal symptoms promptly cleared up as has been the case in the other cases reported. The return of renal function to normal has not been so rapid as in some of the other cases. Six days after operation the excretion of phenolsulphonephthalein was the same as before. The water concentration tests revealed slight improvement in the ability of the kidneys to concentrate fluids. Electrical reaction was not markedly lacking before operation, but it was practically normal a few days after operation. Röntgenograms of bones four weeks after operation did not reveal increase in density.

SUMMARY

A case of hyperparathyroidism in a young girl is described in which symptoms were due to excessive parathyroid secretion caused by a parathyroid adenoma. The symptoms and data include progressive weakness and loss of muscular tonus, attacks of abdominal pain and vomiting, anæmia, polydipsia and polyuria, hypercalcemia and hypophosphatemia, and diffuse decalcification of the skeleton. Data concerning six other proved cases and three not proved by operation were gathered from the literature.

The surgical removal of the parathyroid tumor in the case reported was followed by marked relief from all symptoms.

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