Primary Chief-Cell Hyperplasia of the Parathyroid Glands: A New Entity in the Surgery of Hyperparathyroidism *

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THE IDEA that hyperparathyroidism and an adenoma of a parathyroid gland are synonymous started in 1903, when Askanazy discovered a parathyroid tumor in a patient dying with von Recklinghausen's disease of bone.[2] He called the tumor "an adenoma" and it was such that Mandl sought and removed in July 1925, in a patient with this same bone disease.[12, 13] Until 1933, no other type of anatomic disorder of the parathyroid glands was reported in patients with hyperparathyroidism. In 1934, the condition of primary water clear cell hyperplasia involving all four parathyroid glands was described by Albright, Bloomberg, Castleman and Churchill.[1] The next steps in the understanding of parathyroid pathology were the finding of two adenomas each in a separate gland, carcinoma, and a secondary form of hyperplasia.

Most recently, another type of primary hyperplasia, readily confused with an adenoma when only one gland is examined, has been encountered in ten patients and is the subject of this presentation. In this hyperplasia the cells are chief cells, like those in most of the adenomas. To avoid secondary operations, it has been found essential that chief cell hyperplasia be differentiated at operation from the adenoma, both single and double.

Our experience suggests that this chief-cell hyperplasia will be the common type of parathyroid enlargement in patients with multiple endocrine abnormalities. Four of our ten patients had associated tumors of pancreas or pituitary. Two of these patients have been reported, the parathyroid enlargements being designated at that time as adenomas.[15] Scrutiny of cases with multiple endocrine abnormalities reported in the literature reveal 14 in which the description of the parathyroid enlargement is consistent with chief-cell hyperplasia. The enlargements were variously named (Table 1).

Pathologic Entities and Surgical Practice to the Present

The specific surgical maneuver indicated in a patient with hyperparathyroidism obviously depends upon the type of disorder in the parathyroid glands. In order to understand the surgical significance of the ten cases to be presented in this paper, a review of the experience to date seems helpful. The first 200 patients with hyperparathyroidism operated upon at the Massachusetts General Hospital are chosen for this presentation.

The Single Adenoma. The commonest form of anatomic disorder encountered in hyperparathyroidism is a benign adenoma in one gland with no disease (other than possible atrophy) in the other three glands. The surgical problem in this type is to find the adenoma, remove it, and it alone. To insure the identification of the enlargement as an adenoma, it is more helpful to isolate one of the three undiseased glands than to rely upon frozen section of the adenoma. In the series of 200 cases, 158 such single adenomas have been encountered. (Fig. 1, 2, Table 2.)

The Double Adenoma. An occasional variant of the adenomatous type of the disease is an adenoma in each of two glands, the other two being uninvolved in the dis-

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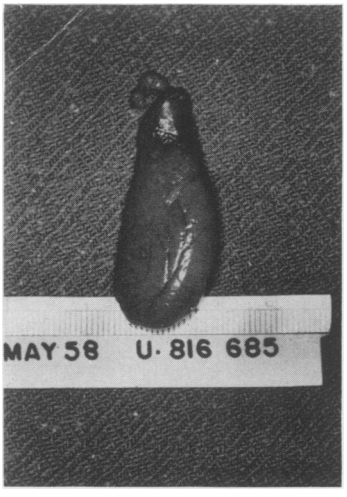
TABLE 1. *Cases in Literature Suspected of Having Chief Cell Hyperplasia*

Author	Date	Autopsy or Operation	No. of Parathyroids Examined	Size	Author's Classification	Renal Disease	Serum Calcium (mg. %)	Serum Phosphate (mg. %)	Bone Disease	Other Endocrine Disease
Claude and Baudouin	1911	A	4	2 kidney-bean, 2 small hazelnut	Multiple adenomas	—	—	—	—	Acromegaly—eosinophilic adenoma of pituitary. Adrenals—17 Gm. Thyroid—190 Gm.—clinical hyperthyroidism.
Cushing and Davidoff	1927	A	3	Slightly larger than normal	Multiple adenomas	Apparently normal	—	—	—	Acromegaly. Colloid goiter. Nodular hyperplasia of adrenals.
		A	2	Central adenoma in each	2 adenomas	Apparently normal	—	—	—	Acromegaly—eosinophilic adenoma of pituitary. Nodular hyperplasia of adrenals. Colloid goiter.
Hanke	1932	A	4	1 hen's egg, 1 walnut, 2 pea	2 adenomas, 2 hyperplasia	Mild disease	23.4	—	Severe osteitis fibrosa cystica	None
Kalbfleisch	1937	A	4	3 pea size, 1 hazel-nut	1 adenoma, 3 hyperplasia	—	—	—	—	Islet-cell adenoma of pancreas.
Washburn	1938	O A	1 2	10.1 Gm. Enlarged	Adenoma Hyperplasia	Severe terminal renal disease	Preop. 19.3 Postop. 16	3.2	Severe osteitis fibrosa cystica	Multinodular colloid goiter.
Rogers *et al.*	1949	A	4	3.88 Gm. total (30 mg. to 2.8 Gm.)	Adenomatous nodules in 3—4th not mentioned	Normal	—	—	Normal	Multiple islet-cell carcinomas of pancreas.
		A	4	2.69 Gm. total (320 mg. to 1.07 Gm.)	Multiple adenomas	Ureterolithiasis, pyelonephritis	—	—	Osteitis fibrosa cystica	Multiple carcinomas of islets of Langerhans.
Woolner *et al.*	1952	A	3	1.51 Gm.	2 adenomas, 1 hyperplasia	Moderate insufficiency	Presumably elevated	—	—	—
		O	4	700 mg.	2 adenomas, 2 not mentioned	Moderate insufficiency	Presumably elevated	—	—	—
Underdahl *et al.*	1953	O	3	2.19 Gm.	4 adenomas in 3 glands	Moderate insufficiency	12.3 to 13.8	2.0 to 2.4	? acromegaly	Islet-cell adenoma of pancreas.
		O	4	720 mg.	Adenomatous hyperplasia in 3 glands	—	10.8 to 12.0	3.3 to 4.1	Acromegaly	Islet-cell adenoma of pancreas.
		A	3	2.3×1.0×1.0 cm. 1.0×0.8×0.8 cm. 1.2×0.5×0.5 cm.	Adenomatous hyperplasia	—	—	—	—	Chromophobe adenoma of pituitary. Nodular hyperplasia of adrenal. Islet-cell adenoma of pancreas.
Wermer	1954	A	4	Markedly enlarged	Nodular hyperplasia	—	12.0	2.7	None	Mixed eosinophilic and chromophobe adenoma of pituitary. Adenomatosis of pancreatic islets. Islet-cell adenoma of duodenum.
McCormack *et al.*	1956	O	4	—	Nodular hyperplasia	—	Elevated	Normal	—	Multiple islet-cell tumors.
		A	4	—	Nodular hyperplasia	—	Presumably elevated	Depressed	—	Multiple islet-cell carcinomas. Chromophobe adenoma of pituitary.
		A	4	—	Nodular hyperplasia	—	Presumably elevated	Depressed	—	Multiple islet-cell adenomas of pancreas.
Fisher and Flandreau	1957	A	3	1.14 Gm.	Nodular hyperplasia	Minimal disease	11.4	2.5	None	Islet carcinoma of pancreas.



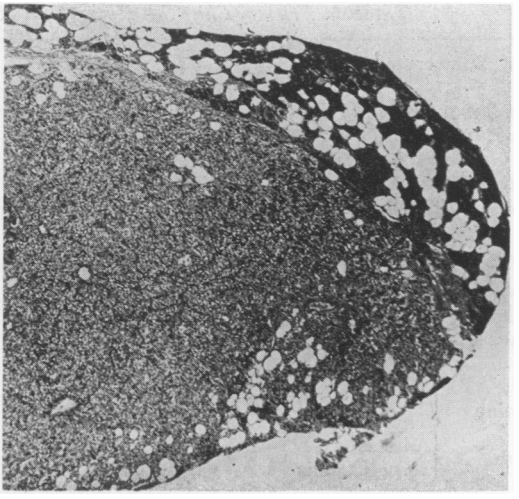


FIG. 1 (Left). A single adenoma of a parathyroid gland.

FIG. 2 (Right). Longitudinal section through part of a parathyroid adenoma showing rim of normal parathyroid tissue. From × 15.

ease process. Resection of both adenomas is needed to relieve the hyperfunction. This type has been found ten times in the 200 cases. In five of the ten, only one adenoma was found at the initial operation and a second exploration was required (Table 2).

Carcinoma. A carcinoma often adherent to surrounding structures was found in eight patients. (Table 2.) Wide resection of the single tumor is performed.[7]

Primary Water Clear Cell Hyperplasia. Hyperplasia involving all four glands, assumed at the time to be a pathologic type comparable to diffuse disease of the thyroid in hyperthyroidism, was encountered in 1933.[1] The surface of the glands is irregular with frequent pseudopods, and their color is chocolate brown (Fig. 3). Microscopically the cells are all of the same type, vacuolated, distended and usually lying in an acinar-like arrangement (Fig. 4). This type has been called primary hypertrophy and hyperplasia and has been found in 14 of the patients (Table 2). A subtotal resection, comparable to subtotal resection of the thyroid in hyperthyroidism, is needed. This has consisted of total removal of three and partial removal of the fourth.[4]

Secondary (Chief Cell) Hyperplasia. The parathyroid glands are found slightly to moderately enlarged in patients with chronic renal insufficiency.[5] An operation is not indicated in this condition, but when the differential diagnosis between primary and secondary hyperparathyroidism has been uncertain, exploration has been done and the glands found to be kidney-bean size, smooth, vascular and grayish rather than brown.

The New Entity

The Finding. In 1952, another entity involving all four parathyroid glands and not previously described was encountered while operating upon a patient with classic hyperparathyroidism (Table 3, 4). Exposing first the right side of the neck a large parathyroid tumor was found behind the thyroid lobe extending down into the poste-

TABLE 2. *Hyperparathyroidism: M.G.H. Series, Pathologic Types of Hyperfunctioning Tissue, 1930 to 1958*

Neoplasia	
1. Single adenoma	158 cases (79%)
2. Double adenoma	10 cases (5%)
3. Carcinoma	8 cases (4%)
Primary Hyperplasia	
4. Water clear-cell type	14 cases (7%)
5. Chief-cell type	10 cases (5%)
Total:	200 cases

TABLE 3. *Primary Chief-Cell Hyperplasia (Clinical Manifestations in 10 Patients)*

Patient Number		1	2	3	4	5	6	7	8	9	10
Sex		M	F	M	F	F	M	M	M	F	F
Age at first operation (yrs.)		43	22	45	50	41	62	38	57	47	47
Dates of operations		1952	1953 1956	1953 1955	1954	1954 1955	1955	1955 1955	1957 1957	1957	1958
Kidney disease	Renal stones		+			+	+		+	+	+
	Nephrocalcinosis	+					+	+			
Bone disease	Classic type	+					+	+			
	Decalcification alone			+	+						
Gastro-intestinal disease	Gastritis	+		+				+	+		+
	Peptic ulceration			+				+			+
	Pancreatitis						+				
	Cholelithiasis						+			+	
Other endocrine gland Disease	Pancreas		+								+
	Pituitary			+			+				
	Thyroid			+	+		+			+	
	Adrenal						+				
	Hypothalamic				+	+					
Mental upsets		+		+				+	+		+
Duration of disease (yrs.)		3	5	12	16	3	1	4	5	2	5
Weights of tissue removed (Gms.) (including both operations where two)		26	1*	2*	2.2	8	1	3*	1*	0.1	0.9

* Estimated.

rior mediastinum. It measured 5.5 cm. in length and was blackish gray rather than brown in color. In a more anterior plane, just below the lower thyroid pole and intimately related to thymic tissue, was a much smaller enlargement of a lighter brown color. It measured 1 cm. in diameter. The opinion of the pathologists were divided concerning the frozen section of both enlargements, adenoma and atypical hyperplasia being the diagnoses. The left side of the neck was then explored and comparable enlargements were found in symmetrical positions. The involvement of all four glands indicated that the process must be a hyperplasia. The disparity in size between the upper and lower glands had been encountered before in the hyperplasias of the water-clear cell type. Both of the large upper glands were resected *in toto* and the lowers only partially resected. Postoperatively the blood calcium level fell to normal in 24 hours (Table 4). Reconsideration of the permanent sections of the four glands suggested a hyperplasia of a chief-cell type. Since this experience, nine other

TABLE 4. *Primary Chief-Cell Hyperplasia (Chemical Manifestations in 10 Patients)*

Patient Number	1	2	3	4	5	6	7	8	9	10
				Preoperative						
Serum calcium (mg. %)	15.6	12.6	13.8	12.0	11.4	11.2	16.0	12.0	12.0	11.2
Serum phosphorus (mg. %)	6.0	1.8	2.2	2.2	2.3	5.2	2.0	2.9	2.7	2.6
Serum alkaline phosphatase (units %)	11	4.4	6.0	3.8	4.9	12	60	2.5	5.8	9.6
Serum N.P.N. (mg. %)	43	21	26	27	27	84	28	32	20	25
Total serum protein (Gm. %)	6.6	5.9	7.1	7.0	5.8	6.5	6.6	7.6	7.1	6.7
24-hour urinary calcium (mg.)	52	437	438	344	294	58	327	186	140	239
				Postoperative (Stable values)						
Serum calcium (mg. %)	8.4	8.0	8.2	8.9	9.0	8.8	9.6	9.4	9.6	*
Serum phosphorus (mg. %)	3.6	3.6	4.0	2.3	3.5	3.6	2.8	3.3	3.1	*

* Operation too recent.

patients have been encountered with the same type of disorder. Curiously all of these ten have been observed in the last 60 patients with hyperparathyroidism, resulting in an incidence of 5 per cent in 200 (see Table 2).

In 1953, the second and third patients with this type of hyperplasia were operated upon, a daughter and a father. Two enlargements were removed at the first operation in both of them and were classified as double adenomas both by surgeon and pathologist.[15] It was not until subsequently when residual hyperparathyroidism was manifest and a second exploration was undertaken that the true pathologic entity was recognized. Following subtotal resection, removal of three and subtotal removal of the fourth, the hyperparathyroidism was relieved. Both of these patients had multiple endocrine abnormalities; the father had also had severe peptic ulceration with hemorrhage leading to total gastrectomy (see Table 3, 4).*

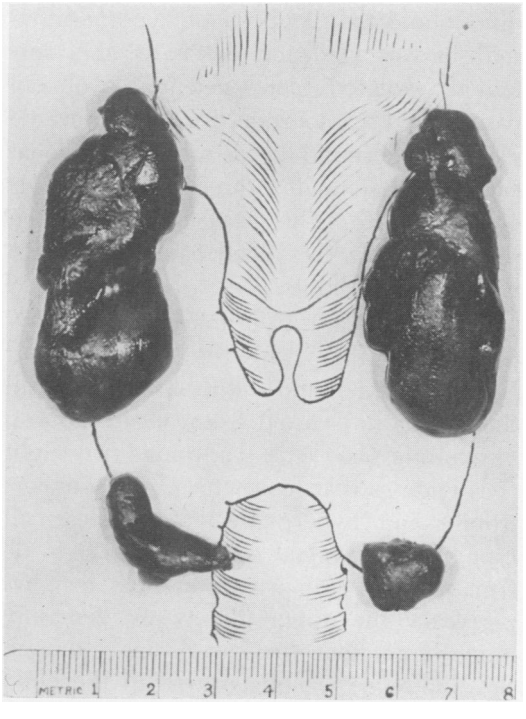


FIG. 3. The four parathyroid glands from a patient with primary water-clear cell hyperplasia. Note the irregular surfaces due to pseudopods. The glands are chocolate brown. The figure shows the disproportion in size between the upper and lower glands.

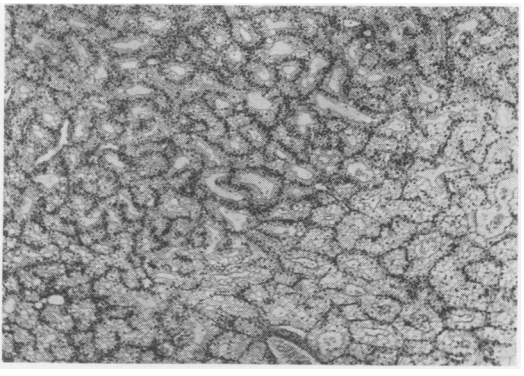


FIG. 4. Primary water-clear cell hyperplasia. The cells are large, vacuolated and with a basal orientation of the nuclei. There is often a well-formed acinar arrangement. From × 76.

During the operation of the fourth patient, the situation was recognized and a subtotal resection was carried out on the four enlarged parathyroids. Hyperparathyroidism had been suspected in this patient for 16 years. She had arthritis in both hips, the exact nature of which is still uncertain, and a tendency to obesity. A thyroid adenoma was also found and resected at the time of the parathyroid operation.

The fifth patient, a woman of 41, had kidney stones. She had been amenorrheic since the age of 23 yet had become pregnant when 29 and had delivered a normal child. She also was obese. On parathyroid exploration, two enlargements were found on the right side. The left side of the neck was not explored and the calcium level failed to fall after operation. On re-exploration six weeks later two comparable enlargements were found on the opposite side; one was removed *in toto* and the other was subtotally resected. The calcium level then fell promptly to normal (Chart 1). At the end of the first operation, both surgeon and pathologist called the two enlargements "adenomas." Following the second operation on this patient, with the descent of the calcium level, we now felt certain that the glands of these patients

* A more detailed account of the ten patients is given in the Appendix.

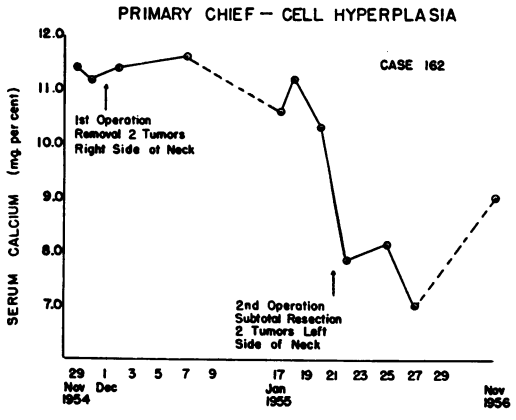


CHART 1. The serum calcium levels in Patient 5 before and after the two operations. The first operation was inadequate; the calcium level promptly fell after the second. The serum calcium levels used are the averages between two independent readings (E.D.T.A. and Fiske methods). Throughout the period of the graph the serum phosphorus level varied between 2.2 and 2.8 mg.%.

constituted an entity to be differentiated both from the adenomas and the water clear cell hyperplasia.

In the sixth patient, a man of 62 with advanced disease of both bones and kidneys, the four enlargements were recognized at operation and subtotally resected. This man subsequently died of advanced renal disease and at postmortem examination nephrocalcinosis, pancreatitis, and an adenoma of the pituitary were found.

The nature of the parathyroid hyperplasia was also recognized in the seventh patient at the initial operation. Four enlargements were isolated and a subtotal resection carried out. The calcium level dropped only slightly following this procedure and at a subsequent operation a much larger fifth parathyroid tumor was disclosed within the thymic capsule in the anterior mediastinum. Following the total resection of this fifth enlargement, the blood calcium level fell promptly to normal.[3]

At operation upon the eighth patient, the true nature of the parathyroid change was not recognized. A single tumor only was resected, and no change of the blood calcium level followed. At a subsequent operation three months later three other hyperplastic glands were uncovered and subtotally resected. The expected fall in blood calcium level followed promptly. It is to be emphasized that not only did the surgeon miss the nature of the disease at the first operation but the pathologist also classified the tumor as an adenoma. The surgeon should have searched further and verified the disease. The pathologist had no alternative since he was offered no other gland by which to compare the enlargement.

The diffuse nature of the hyperplastic process was recognized promptly at the operation of both the ninth and tenth patients. The ninth patient had bilateral staghorn calculi. The four slightly enlarged glands were uncovered and subtotally resected. The tenth patient had had kidney stones and both duodenal and gastric ulcers. She had had a subtotal gastrectomy, and subsequently resection of a stomal and jejunal ulcers. At the second operation an adenoma was removed from her pancreas. This aroused the suspicion of other endocrine disease and the diagnosis of hyperparathyroidism was made on the basis of a sustained, elevated blood calcium level. On parathyroid exploration four hyperplastic glands were found and a subtotal resection carried out removing three and two-thirds of the fourth. This was followed by a prompt fall in the blood calcium level to within normal limits.

The Pathology. In primary chief-cell hyperplasia all the parathyroid glands are enlarged (Fig. 5), and the total weight of all the glands has varied from one to 25 gm. (excluding Case 9).# The range of weight is as wide as that seen with primary hypertrophy and hyperplasia of the clear-cell type,[4] which ranged roughly from 3 to 60 Gm. As with primary water-clear cell hyperplasia, the upper glands are generally much larger than the lower ones, although the difference is not as great in the chief

The four glands in Case 9 were only slightly enlarged. A part of each was used for frozen section before weighing and the total weight was estimated to have been 150 mg.

cell hyperplasia. In some cases, the larger gland on one side has been found in a lower position, and this may be explained by a greater than normal embryological descent of an upper gland. In one patient a gland found in the mediastinum weighed approximately the combined weight of the four glands found in the neck (Case 7).

The glands may have a nodular, irregular contour but, unlike the enlargements in water clear cell hyperplasia, pseudopods have not been encountered grossly. The nodularity in some cases is exaggerated by fibrous septa, and this nodularity with septa seen on cut section provides a clue in the gross diagnosis of the entity.

The color of the glands is tan to reddish-brown similar to that of the adenoma, in contrast to the more chocolate brown of the primary water-clear cell hyperplasia or the creamy-grey of the secondary hyperplasia.

The microscopic picture in primary chief-cell hyperplasia may be indistinguishable from that of an adenoma or secondary hyperplasia, especially at operation where only a small portion of the gland is examined by frozen section. The striking feature in many of the cases is the great variation in the types of cell within a single gland, and this is especially true in glands showing gross nodularity. One whole nodule or an island of cells within a nodule may be composed entirely of small pale chief cells, whereas its contiguous island is made up of large clear cells or oxyphils. (Fig. 6, 7.)

The predominant cell in most of the glands is the small (6–8 μ) or large (8–10 μ) chief cell, in contrast to the huge (10–40 μ) clear vacuolated cell seen in primary water-clear cell hyperplasia. The cell membrane is distinct in most of the larger cells and indistinct in the smaller. The cytoplasm is slightly basophilic in all the cells. The second most common cell is the large pale oxyphil cell, which was the predominant type in two of the cases (Cases 4 and 5). Scattered water-clear cells as well as islands of water-clear cells also occur in some of the glands; and in two cases, if the examination was limited to certain fields one would probably have made a diagnosis of primary water-clear cell hyperplasia. Approximately one-half of the cases have giant cells—large cells with single hyperchromatic nuclei similar to those seen in some of the adenomas. In two cases there were multinucleated giant cells consisting of either chief or oxyphil cells with 3 to 6 small dark nuclei (Cases 5 and 8). Other than the glands that contain giant cells, nuclear variability is minimal. No mitotic figures are present in any of the cells. Basal orientation of the nuclei so characteristic of primary water-clear cell hyperplasia is present only in rare groups of water-clear cells. The same arrangements of cells in cords, sheets, and acini, the latter often filled with colloid-like material, are seen as in adenomas and some cases of secondary hyperplasia.

Fat cells are present in only 40 per cent of the glands, and when present they usually consist of a few cells grouped at one

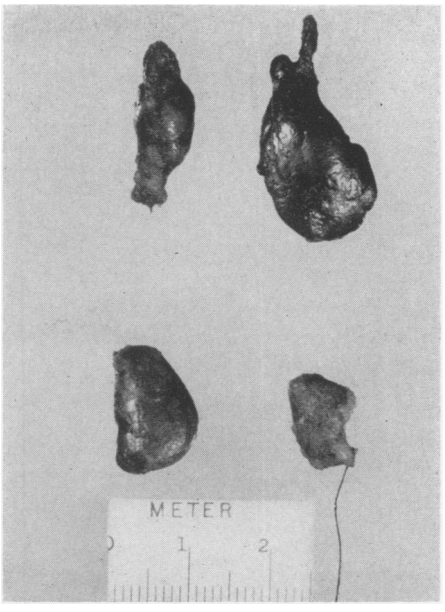


FIG. 5. The parathyroid glands from the fourth patient with primary chief-cell hyperplasia. The glands have the same red-brown color as an adenoma and have a smooth surface unlike the glands in clear-cell hyperplasia with their pseudopods. Usually both upper glands are larger than the lower.

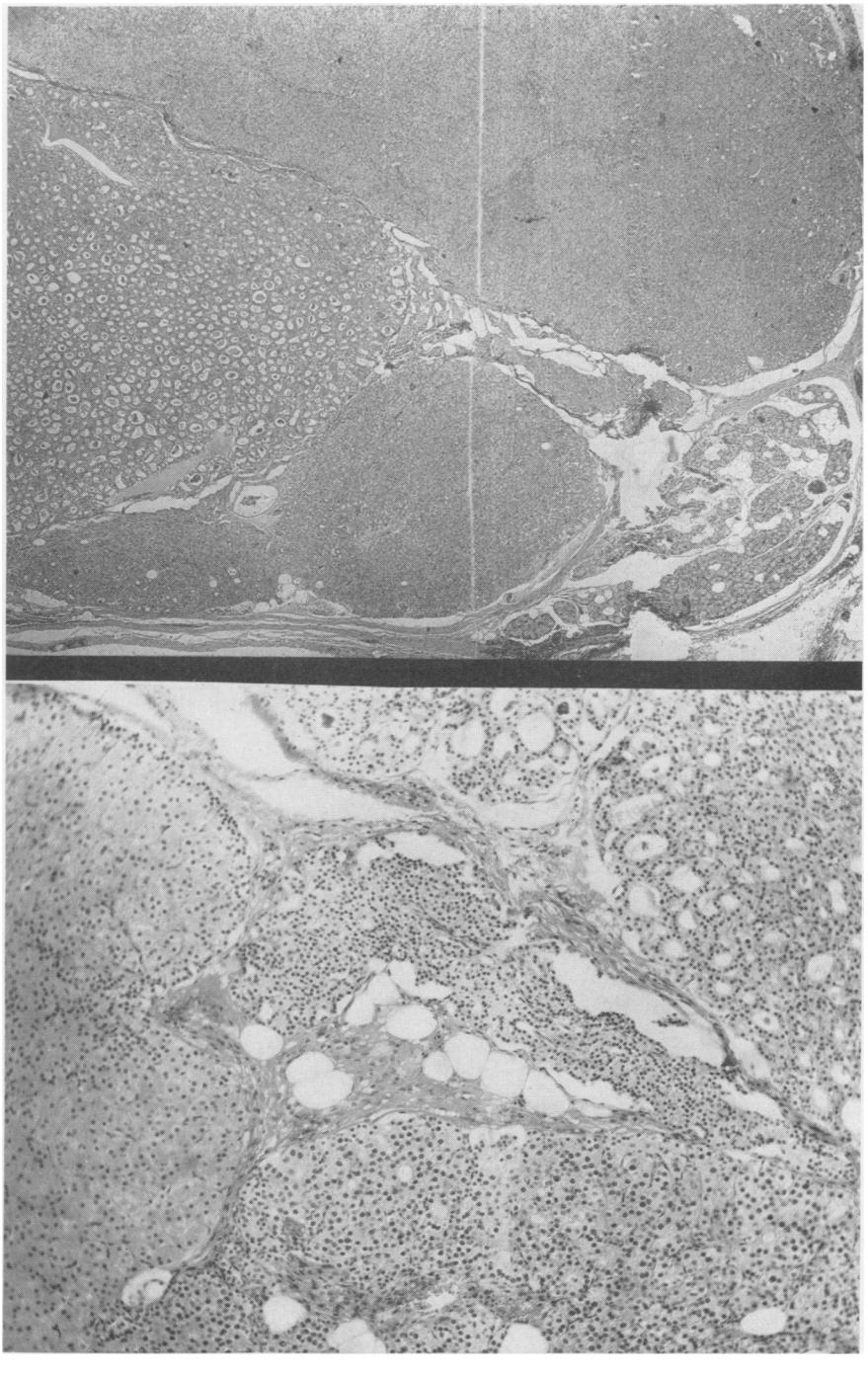


FIG. 6 (Upper). Primary chief-cell hyperplasia. Photomicrograph of a gland from the fifth patient showing the microscopic nodular pattern which is often present. From × 39.

FIG. 7 (Lower). Primary chief-cell hyperplasia. Higher power of part of Figure 6 showing the variation of the cellular pattern. From × 125.

edge of the gland. In one case, however, they were scattered throughout all of the glands (Case 9).

Microscopically, about half of the glands show irregular projections from the surface that resemble the pseudopods described in primary hypertrophy and hyperplasia of the water-clear type. Distinct rims of normal parathyroid tissue, such as is sometimes present in an adenoma, is never present. The normal appearing tissue seen focally in an occasional gland merges indistinctly with the hyperplastic areas.

Clinical and Chemical Evidence of Primary Hyperparathyroidism. From the clinical and chemical point of view the 10 patients had primary hyperparathyroidism. The distribution of the clinical variations is given in Table 3 and the Appendix. The chemical evidence is given in Table 4 including the determinations after operation.

Surgical Treatment. The surgical management of the chief cell hyperplastic glands of the ten patients has been in principle the same as that found successful in water-clear cell hyperplasia.[4] A radical subtotal resection was carried out and proved effective.

The first objective of the surgeon is to identify the pathologic type of parathyroid disorder. If an undiseased gland is the first parathyroid found, then the disease process must be either an adenoma or carcinoma in another gland. If the first gland found is enlarged, it is not sufficient to finish the operation by removing this gland. Before removing it the other gland on the exposed side should be sought. If it is undiseased, the tumor is a neoplasm to be removed. If it is not uncovered, the opposite side is to be explored.

Two enlarged glands may represent two adenomas or hyperplasia and at least a third gland must be found since opinion based on frozen section may be unreliable. If three enlarged glands are uncovered, the fourth is to be found.

The undiseased gland is best identified grossly by meticulous surgery. It is unfair to the patient to remove sufficient part of an undiseased gland (which may be somewhat atrophic) to carry out an adequate frozen section. A snippet for permanent section can be removed from the tip opposite the hilum without damaging the gland excessively. A snippet is too small for frozen section.

When primary hyperplasia is established, whether chief-cell or clear-cell, it has been effective when all of three of the enlargements have been removed and only a small piece of the fourth left with an intact blood supply. A remnant estimated to weigh between 60 and 120 mg. has sufficed in eight of the ten patients. Usually the subtotal resection should be made of the most accessible enlargement so that if too large a remnant is left it can be readily uncovered at a subsequent operation.

Discussion

Review of the first 200 patients with primary hyperparathyroidism treated surgically at the Massachusetts General Hospital reveals that one in five did not have a single benign adenoma. Forty-two of these patients would not have been cured by the removal of a single enlargement believing it to be an adenoma. There were 24 examples of primary hyperplasia, 10 of which were primary chief-cell hyperplasia. This finding is significant to the surgeon because of the ready confusion with the adenoma, single or double. For patients with primary chief-cell hyperplasia a radical subtotal resection of all the glands was required.

Among these 10 patients, failure to recognize the true nature of the hyperplastic process at the initial operation led to a second exploration in four. In a fifth (the seventh patient), the fact that the calcium level failed to fall after the subtotal resection of four glands combined with the knowledge that the process was a hyperplasia led directly to the assumption that a fifth enlarged parathyroid existed. The finding of this fifth abnormal gland, the first on record to our knowledge, accentuates the significance of knowing the type of pathology present. All 10 patients were en-

countered among the last 60 cases, and it is therefore suspected that the incidence of primary chief-cell hyperplasia will ultimately prove to be higher than the present 5 per cent of all cases of primary hyperparathyroidism.

The differential diagnosis between primary chief-cell hyperplasia and adenomas rests primarily on the involvement of all four glands and secondarily on the absence of a rim of normal parathyroid tissue, a finding often seen in the adenoma. Microscopically it is more difficult to differentiate secondary hyperplasia from primary chief-cell hyperplasia. In the latter, there is a tendency toward more nodularity and follicle formation than is usually seen in secondary hyperplasia, and giant cells, which are sometimes seen in this disease, are very rare in secondary hyperplasia. In most cases, however, the differential diagnosis can be made on the basis of the chemical findings, although difficulty may arise in the case of primary hyperparathyroidism with severe renal insufficiency in which the serum calcium and phosphorus determinations may have become reversed. Secondary hyperplasia due to renal disease was excluded in our 10 patients by the elevated serum calcium levels (Table 4).

The ten patients with primary chief-cell hyperplasia from a clinical point of view had typical primary hyperparathyroidism (Table 3). All manifested one or more of the various complications of the disease syndrome—namely, renal calcifications, peptic ulceration and bone changes. A majority also showed evidence of other endocrine abnormalities. The second patient had two insulin-producing islet-cell adenomas of the pancreas, and the tenth had a non-insulin-producing islet-cell adenoma with gross peptic ulceration. The third patient had a tumor of the pituitary with gross peptic ulceration. Four of the patients had pathologic changes in the thyroid gland, and in one of these a small chromophobe adenoma of the pituitary and hyperplasia of one suprarenal gland were also found at autopsy. The fourth and fifth patients were obese, with a tendency to sleep during the day. The fifth patient had amenorrhea for many years before a normal pregnancy at the age of 29 years.

Thus, primary chief-cell hyperplasia should be strongly suspected in patients with primary hyperparathyroidism who have other endocrine tumors; these patients are being encountered with increasing frequency. The parathyroid changes have been interpreted both by us and by previous authors as multiple adenomas, but a review of our cases and those reported in the literature indicates that these changes are more consistent with a hyperplastic than a neoplastic process.

Is this hyperplasia really an entity separate from the water-clear cell hyperplasia or is one a variant of the other? We believe that both types of hyperplasia are different forms of the same process. If compared to the two forms of goitre commonly associated with hyperthyroidism, the uniform microscopic appearance of the water-clear cell hyperplasia indicates that it may be analogous to the primary thyroid hyperplasia of Graves' disease whereas the uneven nodular character of the chief-cell enlargement may be the equivalent of the nodular goitre.

Summary

Since 1952 ten patients with primary hyperparathyroidism have been encountered with a type of parathyroid hyperplasia distinct from the adenoma, carcinoma and the previously described water-clear cell hyperplasia. All of the parathyroid glands are enlarged by the disease process, the cells are predominantly of the non-vacuolated chief-cell type and the entity is being called primary chief-cell hyperplasia. It is essential that the entity be recognized at operation if secondary operations are to be avoided. The enlargements are most readily confused with the adenoma, especially if only one gland is exposed. Five per cent of the first 200 patients with primary hyperparathyroidism cared for at the Massachusetts General Hospital have turned out to have this condition.

Four of the ten patients with this primary chief-cell hyperplasia also had tumors of the pancreas and pituitary gland and it is suspected that this condition, previously described as "adenomatous hyperplasia" and "multiple adenomas," will prove to be the common type of parathyroid disease in patients with multiple endocrine abnormalities.

Grossly the cut surfaces of the individual glands present an ill-defined nodularity, which is more evident microscopically. The gross and microscopic appearance of a single gland may be insufficient to distinguish chief-cell hyperplasia from an adenoma, and examination of all four glands may be necessary to establish a definite diagnosis.

The surgical treatment consists of total resection of three glands and a subtotal resection of the fourth.

Appendix

Case Reports

(See also Tables 3 and 4)

Case 1: (MGH 788215, parathyroid 140). This man was noted to have nephrocalcinosis with a moderate azotemia at the age of 40 in 1949. In 1952, a bone cyst was discovered with a generalized decalcification and absent lamina dura. The serum calcium levels varied between 14.0 and 15.6 mg.% and the serum phosphorus levels between 6.0 and 6.5 mg.%. The serum non-protein nitrogen was 43 mg.% and 24-hour excretion of calcium 53 mg. At operation all the four parathyroid glands were enlarged and showed a primary chief-cell hyperplasia. A radical excision was not carried out in view of the reduced kidney function. In the immediate postoperative period the serum calcium and phosphorus levels became normal though the serum N.P.N. level rose to 100 mg.%. Two years after operation his general health deteriorated and he died in uremia. This man had had several mental upsets in his past as well as a history of gastritis.

Case 2: (MGH 804526, parathyroid 147). This patient, the daughter of the patient in Case 3, had a mild concussion followed by headaches at the age of 17. Five years later, in 1953, following episodes of fainting due to hypoglycemia, two islet-cell tumors of the pancreas were removed. There was a history of passing a few small stones in 1952, and on investigation hyperparathyroidism was confirmed. In 1953 two enlargements of the parathyroid glands were found and resected. In 1956, a further exploration was carried out because of the persistence of hyperparathyroidism, and further parathyroid tissue was removed. The glands showed primary chief-cell hyperplasia.

Case 3: (MGH 538826, parathyroid 148). This man had a partial gastrectomy for duodenal ulcer in 1945, followed by further surgery on two occasions in 1946 for stomal ulceration. He was admitted to the hospital following a convulsion in 1953, at the age of 45. He was a tense gloomy individual and on investigation the bones showed decalcification and the serum calcium and phosphorus levels were typical of hyperparathyroidism. There was a strong family history of peptic ulceration. X-ray showed a further stomal ulcer and a skull film an enlargement of the sella turcica. At operation "adenomas" of the left parathyroid glands were found and removed. Later after a hematemesis a total gastrectomy was performed. No pancreatic tumors were found at this operation. In 1954, a course of radiotherapy was given to the pituitary but with little improvement to his headaches and convulsions. His hyperparathyroidism persisted, and in 1955 the neck was reexplored. On this occasion two parathyroid enlargements were found on the right side of the neck and resected. The right lobe of the thyroid was also removed and showed an adenoma with hyperplasia. After this the serum calcium level fell to normal and has remained there. The parathyroid glands all showed primary chief-cell hyperplasia.

Case 4: (MGH 155884, parathyroid 160). This patient began having pains in the thighs and knees at the age of 20 in 1924. In 1926, x-rays were said to show evidence of infectious arthritis in both hips. In 1938, x-rays of the bones showed demineralization and the serum calcium was 12.4 mg.% and the serum phosphorus 2.6 mg.%. There was a family history of diabetes. In 1949, she was admitted to hospital for bilateral hip arthroplasties—at this time the serum calcium level was 9.6 mg.%—and in 1950 the right side was revised.

In 1954, she was reinvestigated and hyperparathyroidism diagnosed. At this time there was marked obesity and a tendency to fall asleep during the day. At operation four enlarged parathyroid glands were discovered and a subtotal resection carried out. The glands showed primary chief-cell hyperplasia. A nodule was also removed from the thyroid gland which showed hyperplasia. In the postoperative course the serum calcium fell and one month after operation the reading was 8.9 mg.%, and the serum phosphorus 2.3 mg.%.

Case 5: (MGH 868277, parathyroid 162). This patient had right ureteric colic in 1954, at the age of 41. Later a stone was removed from the bladder and an investigation made for parathyroid disease. She gave a history of lassitude, headaches, and easy

fatigability. Her menarche at the age of 16 had been followed by an irregular menstrual flow until the age of 23 when her periods stopped. At the age of 29 she became pregnant and delivered a normal child without recovery of her menses. On examination she was obese and hirsute. The serum chemistries were typical of hyperparathyroidism. The x-rays of the bones were normal. In December 1954 two enlarged parathyroid glands were removed from the right side of the neck. Hyperparathyroidism persisted and in January 1955, a subtotal resection of two further enlarged glands on the left side of the neck was carried out. The glands showed primary chief-cell hyperplasia. Postoperatively the serum calcium fell (see Chart 1) and a year later the level was 9.0 mg.% with a serum phosphorus of 3.5 mg.%.

Case 6: (MGH 879761, parathyroid 165). This patient aged 62 was first seen in late 1954 with increasing weakness, polyuria and anemia. In February 1955, he was admitted to hospital with retention of urine due to a benign enlargement of the prostate. Following decompression of the bladder he was investigated. Bone x-rays showed cysts and decalcification. The serum non-protein nitrogen was 190 mg.%; the serum calcium varied between 10.4 and 11.2 mg.%, and the serum phosphorus between 4.6 and 5.9 mg.%. The 24-hour urinary excretion of calcium was 60 mg. After the non-protein nitrogen level had fallen, an exploration of the neck was carried out and four enlarged parathyroid glands discovered. A subtotal resection was performed and the removed tissue showed primary chief-cell hyperplasia. Postoperatively the serum calcium fell to 9.6 mg.% and the serum phosphorus to 3.5 mg.%. In August 1955, the calcium was 10.3 mg.%, the phosphorus 5.5 and the serum N.P.N. 62 mg.%. The patient died in uremia in December 1955. At autopsy among other findings there were squamous metaplasia of the thyroid gland with an adenoma, a small chromophobe adenoma of the pituitary, and adrenal cortical hyperplasia. There were also nephrocalcinosis and right-sided renal stones. Residual parathyroid tissue was found and showed a more uniform histology than the glands removed at operation.

Case 7: (MGH 824209, parathyroid 170). This man presented with a cyst of the mandible in 1953, at the age of 37. The cyst was removed and the serum calcium level was recorded at 12.5 mg.%. The cyst recurred and on investigation the blood chemistries were those of hyperparathyroidism. There was a four year history of dyspepsia with a gastric ulcer being seen on x-ray in 1951. There had been psychologic upsets necessitating visits to a psychiatrist. The bones showed demineralization but no cysts, and there was moderate nephrocalcinosis. In June 1955, the neck was explored, and four enlarged parathyroid glands were found and subtotally resected. The hyperparathyroidism persisted, and in October 1955, the mediastinum was explored and a fifth enlarged parathyroid removed. The glands showed primary chief-cell hyperplasia. After the second operation the hyperparathyroidism was relieved.

Case 8: (MGH 962888, parathyroid 181). This man had an attack of right renal colic in 1952, at the age of 52 and later passed a small stone. He was admitted for investigation in March 1957, after two further attacks of colic. There was a past history of psychologic upset. From 1945 to 1956 he had regularly drunk two quarts of milk a day and taken alkali for dyspepsia though no peptic ulceration was proved. He had gout. The blood chemistries showed hyperparathyroidism and the x-rays no bone involvement. In April 1957, the right side of the neck was explored and an enlarged parathyroid gland removed. The hyperparathyroidism persisted, and in July, 1957 two enlarged glands were removed from the left side of the neck and the second gland on the right biopsied. All the glands showed primary chief-cell hyperplasia. The serum calcium level fell to normal after the second operation.

Case 9: (MGH 411914, parathyroid 189). This patient, a woman aged 46, was discovered in 1956 to have bilateral staghorn renal calculi. The blood chemistries were typical of hyperparathyroidism, and the x-rays showed no bone involvement. At operation four slightly enlarged parathyroid glands were discovered and subtotally resected. The glands showed primary chief-cell hyperplasia. At operation the thyroid gland was nodular and slightly enlarged. There was a past history of a partial thyroidectomy in 1933 and of a cholecystectomy for gall stones in 1954. Subsequently to the parathyroid exploration the staghorn calculi were removed. In January 1958, the serum calcium was 9.7 mg.% and the serum phosphorus 3.1 mg.%.

Case 10: (MGH 858262, parathyroid 197). This patient passed some gravel in her urine after an attack of right renal colic in 1953. In 1954, at the age of 43 she was treated for a large duodenal ulcer and later underwent a subtotal gastrectomy. In addition to duodenal ulceration there was gastritis and duodenitis. After a period without symptoms she again had dyspepsia in 1956. Following a hematemesis in March 1957, a further subtotal gastrectomy with vagotomy was performed with the discovery of four jejunal ulcers with gastritis, and jejunitis. At this operation a nodule in the pancreas was removed which on histology proved to be a non-insulin-producing islet-cell adenoma. At this point hyperparathyroidism was considered and diagnosed. At a neck exploration

in March 1958, four enlarged parathyroid glands were found and subtotally resected. The glands showed primary chief cell hyperplasia. After this the serum calcium fell to a low normal value. It is still too soon to know what will be the stable postoperative calcium level. Gastric analyses before the first and the second stomach operations did not show a hypersecretion or undue acidity. This patient had a history of long standing mental worries.

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Discussion

Dr. H. A. Frank: We are grateful, as ever, to Dr. Cope and his associates for instruction and guidance in this field.

We encountered a patient recently with whom we could have used Dr. Cope's guidance, I think. This was a 58-year-old man who came to our hospital in November. In 1923, he had had a kidney stone; in 1933, a peptic ulcer. He entered the hospital, having passed another urinary stone, and was found to have the chemical findings of hyperparathyroidism.

In exploration of his neck, these are what we found: (Slide) We thought the right upper parathyroid was a little large, but were not sure it was outside normal limits and did not disturb it. The