PARATHYROID HYPERPLASIA IN CHRONIC RENAL INSUFFICIENCY *

BENJAMIN CASTLEMAN, M.D., AND TRACY B. MALLORY, M.D.

(From the Department of Pathology and Bacteriology, Massachusetts General Hospital, Boston, Mass.)

In contrast with the present universal recognition of the effects of parathyroid abnormalities on the skeletal system relatively little attention has been devoted to the close interrelation of the kidneys and the parathyroid glands. Yet there is reason to believe that instances of the latter are far commoner than the former. For this relation appears to work in either direction. Hyperparathyroidism, if sufficiently long continued, will eventually lead to renal insufficiency because of calcium deposits in the kidney parenchyma, while primary renal insufficiency of a severe and prolonged character will produce parathyroid hyperplasia and — if we accept as evidence the histological alterations in the bones and Shelling and Remsen's [1] parathormone assay of the blood — true functional hyperparathyroidism. Starting, therefore, with either primary lesion a patient may reach an apparently similar end-stage of combined hyperparathyroidism and renal insufficiency. The possibility, therefore, of distinguishing between primary and secondary changes in the parathyroid gland has practical as well as theoretical significance.

In a previous paper describing the pathology of the parathyroid glands in 25 cases of hyperparathyroidism [2] a classification was proposed that divided the lesions sharply into two groups, one in which the changes were restricted to one gland, part of a gland, or occasionally two glands (presumably neoplasia), and a second group in which diffuse hypertrophy and essentially uniform histological changes in all the glands occurred — a condition we classified as hyperplasia. We described furthermore two types of hyperplasia; one in which all the cells are unusually large with clear cytoplasm and nuclei uniformly oriented to the base of the cell (true wasserhelle cells), and another type in which all the glands are composed, except for a scattering of oxyphil cells, of closely packed, normal sized chief cells. A single case of this chief cell type of hyperplasia was

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presented and though it was recorded as being found in a patient with chronic renal insufficiency this relation was not stressed.

In the two and a half year period since our former report 12 new cases of hyperparathyroidism have been seen at the Massachusetts General Hospital. Ten of these were single adenomas, 1 was a wasserhelle hyperplasia, and 1 a chief cell hyperplasia again associated with a long-standing renal insufficiency. No case has been seen that failed to fit readily into the previously described categories and the additional clinical evidence that has accumulated — the absence of a single recurrence of symptoms in the adenomatous group contrasted with several recurrences in the hyperplastic group — strongly substantiates the validity of our classification.

The observation of a second case of pronounced chief cell hyperplasia in association with osteitis fibrosa and chronic renal insufficiency served to emphasize the distinction between the wasserhelle type of hyperplasia — to be called hereafter for the sake of simplicity "primary hyperplasia" even though we realize that it cannot be truly a primary disease of the parathyroids — and the entirely different hyperplasia that is secondary to chronic renal insufficiency. This stimulus led us to study the parathyroids in a group of 29 cases of chronic renal insufficiency and also to search for secondary hyperplasia in other disease states. The present report is a résumé of this study. Our material consists of 2 cases (1 previously reported) of chronic renal insufficiency with bone lesions indistinguishable from those of hyperparathyroidism, 12 cases of chronic glomerular nephritis without bone lesions, 15 cases of renal insufficiency of other types, and an assortment of 9 other cases in which secondary hyperplasia was found. We have included also for purposes of contrast and because cases of this type are still not numerous an additional case of so-called primary hyperplasia.

Review of the Literature

The fact that one or more parathyroid glands may be enlarged in chronic glomerular nephritis or in any form of chronic renal insufficiency is not an original observation. In a paper published in 1935 Pappenheimer and Wilens [3] compared the weights of the parathyroids of normal individuals with those of a group of nephritics and showed quite conclusively that the latter were 50 to 100 per cent heavier. In a later communication Jarrett, Peters and Pappen-

heimer [4] reported the production of enlargement of the parathyroids in rats by a total nephrectomy on one side and partial cauterization of the other kidney. They did not, however, discuss the histological changes in the glands and descriptions of the latter are comparatively rare.

More recently Gilmour and Martin [5] published an exhaustive statistical study of the weights of the parathyroids in a series of 527 cases of varied diseases. They calculated the weight of the parenchyma as distinct from the fatty stroma and from their figures the parenchymatous portions of the glands from the nephritics and renal disease groups were over 60 per cent heavier than the normals. Many of the cases included in their renal group, however, were probably not cases of chronic renal insufficiency so that this figure would certainly have been much higher had cases of the latter only been selected. Here also no histological studies were reported.

In 1905 MacCallum [6] reported a case of chronic glomerular nephritis in which he found one enlarged parathyroid and two apparently normal glands. Bergstrand [7] in 1921 reported 10 cases of parathyroid enlargement associated with chronic renal insufficiency. In 7 of these cases there was a diffuse chief cell hyperplasia of all the glands. In some the gross enlargement was especially marked in one or two of the glands of an individual case but similar histological changes were present in all of the glands. The remaining 3 cases showed enlargement of only one gland, the others being normal in size and structure. In one of this group a rim of normal parathyroid tissue about an apparent adenoma was described. In none of these cases were any clinical data recorded and there was no mention of examination of the bones beyond the statement that one of the cases showed osteoporosis.

The numerous case reports of renal rickets — a disease of children characterized by chronic renal failure usually due to an anomaly in the urinary tract with secondary demineralization of the skeleton — might be expected to provide considerable information relative to the parathyroids. Unfortunately, however, they have not been examined or at any rate described in most of the cases of renal rickets that have been reported. Mitchell [8] in 1930 abstracted 78 cases of renal rickets but makes no mention of the parathyroids in any of them. We have checked most of these case reports and found that many were purely clinical and that in those where autopsies

had been performed examination of the parathyroids was not recorded.

Langmead and Orr[9] in 1933, Smyth and Goldman[10] in 1934, and Price and Davie[11] in 1937 reported cases of renal rickets with diffuse parathyroid enlargement. In Hubbard and Wentworth's[12] case of metastatic calcification and osteitis fibrosa associated with chronic nephritis two parathyroid glands were identified and were said to be hyperplastic though no microphotographs or microscopic descriptions were given.

Shelling and Remsen[1] reported a case of renal rickets in which increased amounts of parathyroid hormone were demonstrated in the blood and in which four enlarged parathyroid glands were found. The description and microphotographs of the glands are identical with our cases of secondary hyperplasia.

Cases of Parathyroid Hyperplasia

A. Primary Hyperplasia

Case 26*: A. T. (35–534), a housewife, aged 57 years, was admitted Jan. 21, 1935. Following three attacks of renal colic she passed a urinary calculus in March, 1931. One month later her right kidney was removed at another hospital. In the summer of 1934 she experienced almost daily attacks of dull pain in the left lower back radiating at times to the groin. During the 6 months prior to admission she had vague aches and pains throughout her body and had lost 15 pounds. Her weight on admission was 83 pounds.

X-rays showed generalized skeletal decalcification with several areas of diminished density in the skull that suggested multiple myeloma. The serum calcium ranged between 14.46 and 16.38 mg. per cent, and the serum phosphorus from 2 to 2.91 mg. per cent. The phosphatase was 4.84 Bodansky units. A bone biopsy showed the changes characteristic of hyperparathyroidism. Renal function tests showed normal excretion by the remaining kidney.

On Feb. 9, 1935, the parathyroid glands were exposed and found to be enlarged (Fig. 1). Both superior and the right inferior glands were entirely removed. Approximately three-fourths of the left lower gland was resected, leaving residual tissue estimated at 0.225 mg. with a good blood supply.

Gross Description: (*Left Upper*): A somewhat flattened, soft, triangular shaped, slightly fluctuant mass 5 by 2 by 3.5 cm. which weighed approximately 6 gm. The surface of the upper two-thirds was purplish red, while that of the lower third was yellowish brown. On section the upper two-thirds was made up of many small cystic

* This is the 26th case in the Massachusetts General Hospital series and the number is used here to correspond with any reference to it in previous or subsequent articles.

cavities 1 to 3 mm. in diameter, from which dark red blood exuded. The lower third was homogeneously yellowish brown.

(*Left Lower*): A smooth surfaced, yellowish brown, encapsulated soft mass measuring 1.5 by 1 by 0.8 cm. which weighed 0.86 gm. The cut surface was uniformly yellowish brown. A portion of this gland was not resected.

(*Right Upper*): An irregularly shaped, encapsulated, lobulated, soft, smooth surfaced mass which measured roughly 3 by 2 by 1 cm. and weighed 3.75 gm. The surface of some parts of the gland was dark purplish red and other parts yellowish brown. One pole was composed of three pseudopod-like projections 1.5, 1 and 1 cm. in length and approximately 1.5 to 1 cm. in diameter. The cut surface was reddish to yellowish brown.

(*Right Lower*): Similar to the left lower, measured 1.8 by 0.7 by 0.3 cm. and weighed 0.59 gm.

Microscopic Examination: A detailed description of this type of hyperplasia was given in our previous paper * but is so perfectly applicable to this case that it will be repeated here in order to compare it with the hyperplasia secondary to chronic renal insufficiency. All the glands have the same appearance. "There is only one type of cell throughout, the wasserhelle cell, which is polyhedral in shape, sharply demarcated by a thin eosinophilic membrane, and varies from 10 to 40 μ in diameter, averaging 15 to 20 (Fig. 3). Many of the cell boundaries are broken, with resultant fusion, similar to the fusion of alveoli in pulmonary emphysema. In contrast with the variability in the size of the cells, the nuclei, though often multiple, are all approximately the same size, averaging about 8 μ in diameter. They are round to slightly ovoid in shape, sharply outlined, moderately hyperchromatic, with an eccentrically placed nucleolus. As a rule the nuclei are located in the end of the cell that is contiguous to the stroma. This produces a characteristic pattern which resembles branches of berries (Fig. 2). The cytoplasm is clear except for a little, light pink-staining granular material. Many of these tiny granules are glycogen deposits. Similar granules are present within the nuclei. There is no fat, except for a rare droplet in the stroma. The low power appearance of the histological sections is so similar to that of clear cell renal carcinomas that distinction would be difficult if the source were not known. The stroma is composed of thin,

* Case 15, pages 7 and 8.

fibrous connective tissue bands containing a moderate number of connective tissue cells and relatively few blood vessels. These bands surround small and large groups of cells, producing a pseudo-glandular effect. This effect is further emphasized by the position of the nuclei, as mentioned above. Occasionally a true single layered alveolus is seen. No oxyphil or chief cells are found. There are no mitoses."

B. Hyperplasia, Secondary to Chronic Renal Insufficiency

Group 1. With Secondary Osteitis Fibrosa and Ectopic Calcification *

F. L. S. (7964)†, a 45 year old American, entered the hospital on Nov. 5, 1935, complaining of painful nodules in his fingers. Twenty-three years before admission he was studied at another hospital for generalized dropsy, was told he had incurable Bright's disease, and was placed on a salt-free, meatless diet. From that time until 2½ years before admission the patient was in apparent good health with no return of edema. Then he began to have itching of the skin, nocturia, and later swelling of his fingers. The positive findings in the physical examination were precordial systolic and diastolic murmurs, cystic swellings on the right forefinger, and firm and tortuous peripheral vessels. The blood pressure was 165/90.

Examination of the urine showed a specific gravity from 1.006 to 1.012, a large trace of albumin and a sediment containing an occasional red blood cell and white blood cell. A phenolsulphonephthalein test showed less than 15 per cent excretion at the end of 1 hour. Examination of the blood showed a red blood cell count of 3,800,000 with a hemoglobin of 65 per cent, and a white blood cell count of 12,000, 63 per cent polymorphonuclears. The non-protein nitrogen was 120 mg. The serum calcium was 10.10 mg. per cent, serum phosphorus 7.92 mg. per cent, and phosphatase 9.36 Bodansky units. The serum protein was 4.9 gm. per cent. X-ray examination showed masses of homogeneous calcification surrounding the proximal interphalangeal joints and along the phalanges of the right second, third and fourth fingers. Both elbows and the acromioclavicular joints showed similar calcified masses. The bones of the pelvis showed slight decalcification. The skull was riddled with small areas of decalcification. In all the films the large and small blood vessels showed marked arteriosclerosis with calcification, some of them definitely of the Mönckeberg type. A pyelogram showed extremely small kidneys.

While on the ward during the 3rd week he was suddenly seized with severe pain between the shoulder blades and later the pain was localized in the left anterior chest and upper abdomen. He developed bundle branch block; the blood pressure fell to 60/50 and he died 5 hours later.

* One similar case was reported in our previous paper,[2] Case 23A, page 12.

† A clinical discussion of this case has been reported separately by Dr. Fuller Albright in the *Tr. A. Am. Physicians*, 1936, **51**, 199–212. This case has also been reported in the Case Records of the Massachusetts General Hospital, *New England J. Med.*, 1936, **214**, 320–325.

Postmortem examination showed in addition to the parathyroid enlargement a marked chronic glomerular nephritis, metastatic calcification around joints, calcification of the coronary, renal and splenic arteries, coronary occlusion, and rheumatic heart disease with mitral stenosis. Death was due to coronary thrombosis. Sections of the various bones showed a mild to moderate degree of decalcification and osteitis fibrosa (Fig. 9). The latter was indistinguishable from the bone lesions in primary hyperparathyroidism, except that no cysts were present.

Gross Description: All four parathyroid glands were in their normal position. They were all enlarged, firm, yellowish white, and somewhat lobulated (Fig. 4). The cut surface was uniformly yellowish white and smooth. (Note the absence of any brown color, a finding that is present in normal glands, adenomas, and primary hyperplasias.) In one gland a calcified nodule was found. The right lower was the largest, measured 2 by 1.5 by 1.5 cm., and one-half of it weighed 2 gm. From the weight of this half the weights of the glands were estimated as: right lower 4 gm., left lower 3 gm., and the upper glands 2 gm. each.

Microscopic Examination: The picture here is almost identical with that of the case of chief cell hyperplasia described in our previous paper. None of the architectural features of a normal parathyroid gland can be made out. Instead of anastomosing columns of epithelial cells separated by bands of fibrous stroma containing large fat cells, the tissue consists of an almost solid sheet of epithelial cells punctuated only by vascular channels at rather regular intervals with very scant fibrous stroma chiefly limited to the adventitia of the blood vessels (Fig. 8). Practically no fat cells are present. The structure is by no means uniform, however, for even with low power it is evident that there are circumscribed islands of varying size often encapsulated with a delicate band of collagen. Either a peculiarity of the arrangement of the cell cords or a consistent variation in the cells themselves serves to mark the islands clearly from the surrounding tissue (Figs. 5 and 6). Throughout the great majority of the gland the predominant cell is the chief cell, a trifle more vacuolated than normal, but with a cytoplasm by no means totally clear. Within each of the circumscribed islands which have been mentioned the cells tend to be very similar in appearance but between one island and another there may be marked variation

(Fig. 7). In one, for instance, the cells are uniformly large and tend to show a high degree of vacuolization sometimes approaching the appearance of the wasserhelle hyperplasia, though the largest cells observed are only half the size of those characterizing that condition. In this same island numerous small acini are found with a granular serous secretion in their lumens. In other islands the cells show less than normal vacuolization of the cytoplasm but the nuclei are a little large and distinctly hyperchromatic. A columnar architecture (obscured throughout most of the gland) is rendered prominent by a widening of the vascular channels and an increase in the collagenous stroma. In still another localized area cystic spaces often filled with red cells but without an endothelial lining are seen. This appearance is one we have noted in chief cell adenomas. Occasionally within one of these islands smaller secondary islets can be made out. About the periphery of the larger islands a zone of smaller, more compactly arranged cells is suggestive of compression from the growth of the island itself.

Scattered throughout all the gland singly, in small clusters, and in large nodules, are cells with oxyphil granules in their cytoplasm (Fig. 7). The cells vary in diameter from that of a normal chief cell to three times this size; the granules may be sparsely scattered or so densely packed as to make the cytoplasm apparently homogeneous; there may be extensive vacuolization or there may be none. The nuclei vary from vesicular to pyknotic. In short, the entire gamut of transition stages from chief cell to fully developed oxyphil is present.

A review of the histological features of Case 23A in our former paper, the chief cell hyperplasia with chronic pyelonephritis and osteitis fibrosa, shows that they are in all essentials similar to those of this case. The hyperplasia is diffuse throughout all the glands, the predominant cell is the chief cell; rare acinar formation and occasional wasserhelle cells are observed, whereas transitional and fully developed oxyphils are very numerous. It likewise shows clearly developed islands in which one or another type of cell predominates and around which the surrounding gland tissue seems compressed.

Group 2. Chronic Glomerular Nephritis Without Secondary Bone Involvement

This group is comprised of 12 successive cases of chronic glomerular nephritis in which the parathyroids were available for study.

The pertinent clinical and postmortem findings are summarized in Table I. The duration of symptoms, as far as this can be estimated from the clinical histories, has been given, though a glance at the weights of the kidneys makes it apparent that the renal disease must

TABLE I

Chronic Glomerular Nephritis

No.	Age	Duration	Non-protein nitrogen	Calcium	Phosphorus	Parathyroid			Combined weight of kidneys
						No.	Size	Weight	
	yrs.	*mos.*	*mg./%*	*mg./%*	*mg./%*		*mm.*	*mg.*	*gm.*
1	24	11	200	..	..	2	Normal	..	120
2	30	6	300	..	..	4	8×4×3, 15×8×4 12×5×2, 14×10×4	105, 293 125, 340	75
3	32	8	127	6.35	5.70	4	12×8×5, 3 normal	863	125
4	42	12	180	..	..	4	15×1×4, 8×6×3 2 normal	..	60
5	19	18	205	..	..	4	12×6×3, 9×4×3 10×8×4, 11×8×2	630	100
6	52	12	120	..	..	4	Normal	..	270
7	30	7	190	8.44	8.40 14.42	3	Sl. enlarged	..	150
8	56	30	220	5.91	16.0	4	8×5×4, 3 normal	..	150
9	25	11	105	8.94	5.32	3	1 sl. enlarged 2 normal	..	170
10	26	15	265	8.09	15.65	4	8×5×2, 8×4×3 10×5×2, 7×5×3	360	225
11	26	36	250	7.52	12.13	4	Each 1.2×0.5×0.3	846	120
12	39	16	250	..	..	4	1 sl. enlarged 3 plump	..	240

in most instances have been far more chronic than the symptoms would indicate. They are evidently as a group, however, of distinctly shorter duration than the cases in the preceding group and this undoubtedly accounts for the absence of bone pathology. The vertebral bone marrow was examined in all these cases and found to be negative, except in one which showed slight degrees of bone re-

sorption without, however, any evident fibrosis. The levels of blood calcium and blood phosphate where available are worthy of note. Without exception the calciums are low and the phosphates moderately to markedly elevated, in contrast with the exactly reverse condition — high serum calcium and low serum phosphorus — found in primary hyperparathyroidism.

In this group of cases all but 2 showed gross enlargement of one or more of the glands. In 5 cases enlargement of all the glands was noted (Fig. 10), in 3 cases it was evident in only one, and in 1 case two were enlarged and two were normal. These gross findings are very similar to those of Bergstrand.[7]

With microscopic examination, however, our findings become different. We have found in all of the glands of every case in this group what we consider definite evidence of hyperplasia. Since this hyperplasia is admittedly in some of the cases rather slight, it becomes necessary to examine the criteria on which a diagnosis of hyperplasia can be made.

Let us recall for a moment the architectural features of the normal gland. It possesses a structure rather common among the endocrine glands of anastomosing columns of epithelial cells surrounding vascular spaces which are usually a little wider than ordinary capillaries and approach the character of sinusoids. But in the parathyroids this columnar structure is more complicated than in the other endocrine glands in that it is doubled. Cords 2 to 4 cells wide anastomose about the smaller vascular channels but these are in turn grouped into larger columns 4 to 20 cells in width, which in turn anastomose about the larger vessels and the fibrous stroma of the organ, a stroma, moreover, that is unique among the endocrine glands in that large fat cells are normally present in it in considerable numbers at all times after puberty.

With progressive grades of hyperplasia these fat cells steadily decrease in number and eventually may even disappear. They appear to behave essentially like the fat cells of the bone marrow, modestly giving way to the more important parenchymal cells as need arises. This would explain why some hyperplastic glands are not increased in size, *i.e.* the hyperplasia has progressed only to the point of fat displacement.

The proportion of fat cells to parenchyma, although a very important aid, is by no means an entirely satisfactory criterion since

the "normal" proportion of fat is far from constant, varying significantly with age. Probably the next most useful yardstick is the character of the epithelial columns. Although under normal conditions these show a wide range of variation from 4 to 20 or more cells in thickness, the majority run from 4 to 12 and the thicker ones are found only in limited portions of a gland. With hyperplasia, more and more of the columns are found in the upper ranges and solid sheets of cells without discernible columnar arrangement appear (Fig. 11). Not merely the fat cells but even the fibrous stroma tends to disappear. This widening of the epithelial columns and progressive diminution in the fat and even the fibrous stroma produce a decided compactness of the tissue which is obvious at a glance with low magnification. Though small compact areas may be found in some presumably normal glands, the extension of this appearance to any large proportion of the gland certainly indicates hyperplasia.

Finer cytological details have proved of relatively little help. In the early stages of hyperplasia a tendency to increased vacuolization and simultaneously an increase in the glycogen content, as judged by Best's carmine reaction, is apparent, but with the more marked degrees the cells tend to become smaller once more and most of them revert to the typical chief cell appearance. The search for mitotic figures has, as in the case of the adenomas, proved disappointing. Even in the most extreme hyperplasia — a hundredfold increase in the amount of parathyroid tissue — a 20 minute search with an oil immersion lens has failed to reveal one.

For the sake of clarity the following tabulation of our criteria for the diagnosis of chief cell (secondary) hyperplasia seems worth while.

Criteria for the Diagnosis of Chief Cell Hyperplasia

Gross Appearance:

(*A*) *Size:* Characteristically slight to moderate enlargement of all glands rarely reaching the size of the usual adenoma or primary hyperplasia; however, marked variation is not infrequent in the size of the individual glands of a given case and one or all of them may even be normal in size.

(*B*) *Color:* The glands tend to be a creamy gray rather than an orange-brown.

(*C*) *Consistence:* The glands are firmer and much less pliable than the normal gland, the adenoma or the primary hyperplasia.

Microscopic Appearance:

(*A*) *Low Power*

1. Uniformity of all glands in a given case.
2. Absence or marked decrease in intercellular fat cells.
3. Increase in number of cells as shown by widening of the epithelial columns.
4. Development of compact areas in which columnar arrangement is no longer distinguishable.
5. Tendency to acinar arrangement in the more advanced cases.
6. Uniformity of the whole gland except in the more advanced cases where there is a tendency to adenomatous-like and papillary formations without real encapsulation.

(*B*) *High Power*

1. Cells are *normal sized* chief cells, unlike the adenoma or primary hyperplasia.
2. Tendency to vacuolization of the cytoplasm in less severe cases producing slight cell enlargement.
3. No mitoses or hyperchromatism.
4. Oxyphil cells more numerous than expected for age of individual (Fig. 12).
5. Glycogen content slightly higher than adenoma or primary hyperplasia.

Judged on such criteria none of the 12 cases in this group fails to show some evidence of hyperplasia, though in 2 of them it is but slight — not greater than that to be observed in the succeeding group of cases. In the individuals in the present group where gross enlargement was present in one gland only, evident hyperplastic changes have been observed microscopically in the normal sized glands as well and except in degree there has been no difference between the small and the large glands. As compared with the preceding cases with bone involvement, the picture also differs only in degree, the persistence of a few fat cells, and a slightly less degree of island formation and acinar arrangement.

Group 3. Mild Degrees of Secondary Hyperplasia

In a review of the microscopic slides of the parathyroid glands removed from 300 routine autopsy cases (excluding chronic glomerular nephritis), we were able by the use of the criteria listed above, without knowing the anatomical or clinical diagnoses, to select 23 cases in which we believed there was definite hyperplasia. Fourteen of these cases showed, both clinically and pathologically, evidence of some degree of renal insufficiency. Eight of the 14 cases were on the Genito-Urological Service for pyelonephritis; the 9th was a case of congenital polycystic kidneys; the 10th, multiple myeloma with renal involvement; and the last 4 were cases of vascular nephritis. One of the latter had malignant nephrosclerosis of one kidney, the other kidney being atrophic with its pelvis and ureter obstructed by gritty calcified material. The pertinent findings in these cases are given in Table II.

The parathyroid glands removed from the case of polycystic kidneys were surprisingly normal in size. Only two were found and unfortunately they were not weighed. Both of these, however, are alike histologically. There was almost complete disappearance of the intercellular fat cells. Except for occasional single and small groups of oxyphil cells, the glands were composed of chief cells of the transitional wasserhelle type, *i.e.* cells that are on their way to wasserhelle cells. These cells were larger than the normal chief or even oxyphil cell, but did not reach the size of the large wasserhelle cell seen in primary hyperplasia.

One of the 9 cases of pyelonephritis, No. 15 in Table II, showed evidence of very early osteitis fibrosa with characteristic dissecting resorption of the spongiosa, as described by Schmorl [13] and Jaffe.[14] This case might, therefore, fit into the group of renal rickets or our Group 1, but because of the mild degree of bone change, when compared to the other 2 cases, we have preferred not to include it in the renal osteitis fibrosa group.

The remaining 9 cases were not cases of renal insufficiency. Three, however, had bone disease which probably accounts for the secondary parathyroid changes — rickets, metastatic carcinoma and Paget's disease. Whether the latter can really be responsible for the parathyroid hyperplasia is questionable. Two of the cases had duodenal ulcers. One of these, however, showed pituitary basophilism which may account for the parathyroid changes. One of the

TABLE II

Mild Degrees of Secondary Hyperplasia

No.	Age	Duration	Non-protein nitrogen	Phenol-sulphone-phthalein	Calcium	Phosphorus	Parathyroid		Anatomical Diagnoses
							No.	Size	
	yrs.	*yrs.*	*mg./%*	*%*	*mg./%*	*mg./%*		*mm.*	
1	57	¾	36–135	..	..	..	3	2 normal 1 sl. enlarged	Carcinoma of bladder. Pyelonephritis
2	62	5	280	5	..	..	2	1½ normal	Prostatic hyperplasia. Pyelonephritis
3	57	12	81	..	9.79	3.38	4	Normal	Renal stones. Pyelonephritis. Carcinoma of bladder
4	52	31	128	..	..	..	1	Twice normal	Renal stones. Pyelonephritis
5	59	20	..	0–5	9.76	7.90	4	Slight ++	Atrophy of left kidney. Malignant nephrosclerosis of right. Nephrolithiasis
6	49	3	86	Trace	5.2	9.1	2	Normal	Polycystic kidneys
7	35	10	210	5	8.48	11.76	2	1 normal, 6×4×3	Benign vascular nephritis
8	30	6½	88	Trace	..	..	2	1 sl. enlarged. 1 normal	Pyelonephritis
9	58	¼	53	25	9.40	4.96	4	All 8×5×3	Multiple myeloma
10	44	8	66	0–3	..	..	3	Normal	Hydronephrosis. Neurogenic bladder
11	39	?2	220	..	8.81	15.66	3	Twice normal	Malignant vascular nephritis
12	32	10	80	..	7.7	6.4	1	Normal	Benign vascular nephritis
13	54	1½	31	..	..	..	2	Normal	Pyelonephritis
14	27	3½	20	25	..	..	1	Normal	Nephrolithiasis. Pyonephrosis
15	17	3	150	5	..	..	4	Twice normal	Congenital anomalies of bladder and ureters

remaining 4 cases had malignant hypertension with slight chronic vascular nephritis, but with a non-protein nitrogen of only 24 and a phenolsulphonephthalein of 40 per cent, it was felt that this case did not belong with the group of renal insufficiency cases. The remaining 3 cases — bronchial asthma, rheumatic heart disease, and metastatic carcinoma of the lung from a carcinoma of the cecum — showed nothing in the kidneys that could be responsible for the parathyroid changes. Table III gives abstracts of the cases in this group.

TABLE III

Hyperplasia in Non-Renal Cases

No.	Age	Parathyroid		Anatomical Diagnoses
		No.	Size	
1	*yrs.* 12	1 (operation)	Normal *mm.*	Rickets
2	36	..	...	Oat cell carcinoma of lung with metastases to bones
3	64	4	Normal	Paget's disease of bone. Glioma
4	67	3	2 normal. 1 (8×5×4—80 mg.)	Duodenal ulcer, gastritis, pituitary basophilism
5	55	3	Normal	Duodenal ulcers for 25 yrs. Had taken soda bicarbonate for yrs.
6	42	3	Normal	Hypertension. Chronic vascular nephritis, slight
7	65	1	Normal	Rheumatic heart disease
8	64	3	Normal	Bronchial asthma
9	33	4	Normal	Metastatic carcinoma of lung from cecum

On gross examination most of the glands in this group showed very slight but definite enlargement. The microscopic picture, however, was similar to but not so pronounced as most of those in the group of chronic nephritics. Here, intercellular fat cells were more numerous in some of the glands, but others showed a definite compactness of structure, vacuolization of cells and pseudoglandular arrangement.

Discussion

The exact mechanism of the parathyroid hyperplasia in chronic renal insufficiency is still a subject of active debate and no attempt will be made to discuss it here. Phosphate retention, however, is generally admitted to be the initial stimulus and this concept has recently been supported by the production of parathyroid hyperplasia in rabbits by Drake, Albright, and Castleman [15] by the repeated injection of a neutral buffered isotonic solution of sodium phosphate. The hyperplasia so produced is essentially similar to that described in this paper, being characterized by a great increase in the number of chief cells, chief cells, moreover, of normal size and appearance. The only significant difference lies in the lack of oxyphils in the experimental hyperplasias. This may depend on a species difference or may merely be due to the fact that the experiments were not of sufficiently long duration.

Our cases have been presented in four groups: (1) marked chronic renal insufficiency associated with osteitis fibrosa; (2) chronic glomerular nephritis; (3) milder degrees of renal insufficiency; and (4) a group of 9 cases showing parathyroid hyperplasia but without any degree of renal insufficiency. In the first group in which the hyperplasia was most marked and in which bone lesions were also present we have reliable clinical data pointing to a state of severe renal insufficiency of many years duration. In the next group, chronic glomerular nephritis, the duration of the renal insufficiency as judged by the clinical history and by the degree of renal atrophy was also marked but not so great as in the first group. Correspondingly the degree of parathyroid hyperplasia was not so great. The third group presented, showing minor grades of hyperplasia, was made up of a variety of types of renal pathology including nephrosclerosis, polycystic kidneys and pyelonephritis, for the most part secondary to other pathological conditions in the male genito-urinary tract. Although nephrosclerosis and polycystic kidneys represent very long-standing renal disease, functional renal insufficiency is apt to appear only in the terminal stages and to be of comparatively short duration. The fact that all of our cases of chronic glomerular nephritis showed parathyroid hyperplasia appears at first hand quite at variance with Bergstrand [7] who found hyperplasia in only 20 per cent of his nephritics. His paper, however, includes no clinical data and, so far as the negative group is concerned, no classification as regards

types and severity of nephritis from which an estimate of the degree and duration of renal insufficiency can be made.

The studies which we have reported in our previous paper combined with these just presented indicate that histological examination of the parathyroid glands will ordinarily readily permit the distinction between primary and secondary hyperparathyroidism. Primary hyperparathyroidism is the result either of a tumor-like enlargement of one or part of one gland, or of a diffuse hyperplasia of all the glands, sharply characterized by the uniform wasserhelle character of all the cells. Secondary hyperplasia, in contrast, though likewise showing as a rule uniform and sometimes marked enlargement of all the glands, fails to show the same orientation of all the cells toward one line of differentiation. Though chief cells greatly predominate, wasserhelle cells, although much smaller than those seen in primary hyperplasia, are by no means totally suppressed and oxyphil cells are regularly greatly increased in number. With adequate data confusion between these two types of hyperplasia is scarcely possible. However, in view of the inadequate data of many of the cases in the literature, and before we realized the difference in histology and clinical findings, we undoubtedly erred in interpreting some of them.

In our previous paper in the classification of the cases reported in the literature we listed 14 cases of wasserhelle cell hyperplasia and only 2 cases of chief cell hyperplasia. We also listed 10 cases of multiple adenomas of the parathyroid. A review of these 26 cases in light of our further knowledge on the subject calls for a definite reclassification. Probably not more than 5 out of the 14 listed cases of primary hyperplasia really belong to this group. Many of the others belong to the secondary chief cell type, but the majority cannot be accurately classified because of insufficient data. This same criticism might be applied also to some of the 11 cases cited from the literature in the paper by Albright, Bloomberg, Castleman and Churchill [16] in the first report of primary hyperplasia.

A review of the literature, however, suggests the possibility of confusion with the primary adenomas since enlargement of a single gland in association with nephritis has been described on several occasions. Most of these reports are based solely on gross examinations and some of Bergstrand's findings agree with ours — that significant grades of hyperplasia may be present without enlarge-

ment of the gland. It seems fair to assume that in many of these cases histological examination would have revealed significant changes in the other glands.

That a primary parathyroid adenoma should occasionally be found in a patient suffering from chronic nephritis is by no means impossible and it seems probable that MacCallum's [6] case is to be explained in this way. Dr. Fuller Albright has reviewed this case with Dr. MacCallum. They found true osteitis fibrosa and felt that the case was one of a true parathyroid adenoma.[17] Seven of Bergstrand's 10 cases evidently correspond to ours in all essentials. In the remaining 3 enlargement was limited to one gland; the remaining glands were examined histologically and were considered normal. In 1 of these cases, moreover, the abnormality was limited to an adenomatous growth in only a part of the gland. Any doctrinaire opinion of these findings is obviously unwarranted. It is possible that minimal grades of diffuse hyperplasia were overlooked but it is also remotely possible that localized, adenoma-like hyperplasia is occasionally the response of the parathyroid glands in secondary hyperplasia. A tendency in this direction — toward the development of localized, apparently semi-autonomous centers of excessive growth or of peculiarities of differentiation — has been described in our 2 most advanced cases. However, in these instances obvious hyperplasia was evident in the remainder of the gland and also in each of the other glands from the same case, and, moreover, in all of the 38 cases included in this report, not merely those associated with renal insufficiency, hyperplasia when present in one gland was also evident in all the other glands from the same patient. We are, therefore, prejudiced against the occurrence of localized hyperplasia. The study of a much larger amount of material will evidently be necessary to reach a conclusion on this point.

The cause of the gross enlargement of the parathyroid tissue in the various types of hyperparathyroidism has aroused some conflict of opinion. In primary hyperparathyroidism of both the adenomatous and the hyperplastic types a tendency to enlargement of individual cells is very evident. Some authors have felt that this macrocytosis alone without an increase in the number of cells was adequate to explain any grade of enlargement they had seen. As far as the adenomas are concerned it certainly would be difficult to explain a tumor such as that in Case 1 of the Massachusetts General

Hospital series. This tumor weighed 53.2 gm. and although occasional large cells (30 μ) are present, the average cell is not over 15 μ in diameter. Macrocytosis may explain a tenfold increase in size but hardly a thousandfold one. Another element tending to increase the gross mass of the glands is the presence in them of dilated acini and cysts containing fluid. In some of the adenomas and most of the primary hyperplasias this must be a significant factor in the weight of the glands. Quantitative studies of the influence of these two factors in relation to the adenomas and especially to the primary hyperplasias are in progress and any opinion would be hazardous without such data.

In the secondary hyperplasias, however, there is no room for argument. The degree of glandular enlargement may run close to a hundredfold, as in 1 of the cases presented, but the predominant cell is a normal sized chief cell and, though larger water-clear and oxyphil cells are present, they are not numerous enough to affect the size of the glands significantly. Moreover, acinar formation is limited and acini where present show small lumens without significant accumulation of fluid. Yet even in these cases where an extraordinary multiplication of cells must have taken place mitotic figures have not been observed.

In our former paper an attempt was made to infer from the cytological evidence presented the probable interrelations and functional significance of the three main types of cells that make up the normal parathyroid. Does the study of secondary hyperplasias carry us any farther in this direction? As regards the interrelation of the cells, it is strongly confirmative of the monophyletic theory. In the normal glands and in the adenomas the fundamental cell was found to be the chief cell and all stages of transitional steps between it and the water-clear cells and the oxyphils were noted. In normal glands such transitional cells must frequently be searched for, but in the active, highly cellular secondary hyperplasia they are extremely numerous, particularly highly vacuolated cells with considerable dense acidophilic cytoplasm which show characteristics of both the water-clear and the oxyphil cells.

The findings in this group of cases appear to fit the hypothesis of a slow progression of development from the chief cell, through the water-clear to the oxyphil. The possibility of direct development of oxyphils from the chief cells cannot be excluded however. We

would suggest that in secondary hyperplasia the rate of this progression is increased, thus accounting for the much greater number of oxyphils than would be expected for the age groups of the patients. The presence of large numbers of oxyphils would on this basis interfere in no way with the theory previously advanced — that they are essentially functionless — since the greatly predominant chief cells would account for the presumable increase in function.

Summary and Conclusions

Another case of "primary" hyperparathyroidism characterized by diffuse hyperplasia of the parathyroid glands of the wasserhelle type is reported. The histological findings in this case have been used to emphasize the contrasting character of the "secondary" hyperplasia which is described in detail on the basis of 29 cases of chronic renal insufficiency of varying grades. Whereas in the primary hyperplasias a uniform direction of differentiation of all cells to the large water-clear type is the invariable finding, in the secondary hyperplasias such uniformity is lacking. Here the glands are composed almost completely of normal sized chief cells, although a few small water-clear cells are occasionally present. The oxyphil cells are always greatly increased in number. The glands show varying degrees of gross enlargement and even when the enlargement is limited to a single gland, microscopic examination has not failed in any instance to show evident hyperplasia in the other glands as well. The criteria for the diagnosis of secondary hyperplasia are described. Comparison of cases of chronic renal insufficiency with and without bone lesions showed quantitative but not qualitative differences in the parathyroid glands, and the development of osteitis fibrosa is felt to be directly dependent on the duration of renal insufficiency. That these changes are in no way specific to renal insufficiency is shown by the fact that no qualitative differences could be recognized between the milder grades of secondary hyperplasia in nephritis and those occasionally seen in individuals without renal insufficiency, but with a variety of associated lesions varying from metastatic carcinomatosis involving bone to basophilism of the pituitary.

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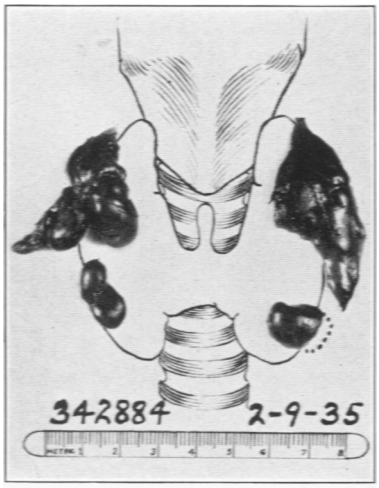
DESCRIPTION OF PLATES

PLATE 89

FIG. 1. A diagrammatic drawing of the parathyroid glands *in situ* from a case of primary hyperplasia. Note the pseudopod-like projection in the upper glands.

FIG. 2. A microphotograph of a section of one of the glands in Figure 1 showing the basal orientation of the nuclei producing a characteristic pattern. × 500.

FIG. 3. A microphotograph of a section of one of the glands from the same case and at the same magnification. The large wasserhelle cells show a definite tendency to glandular arrangement. Note the resemblance to the hypernephroma cell. × 500.



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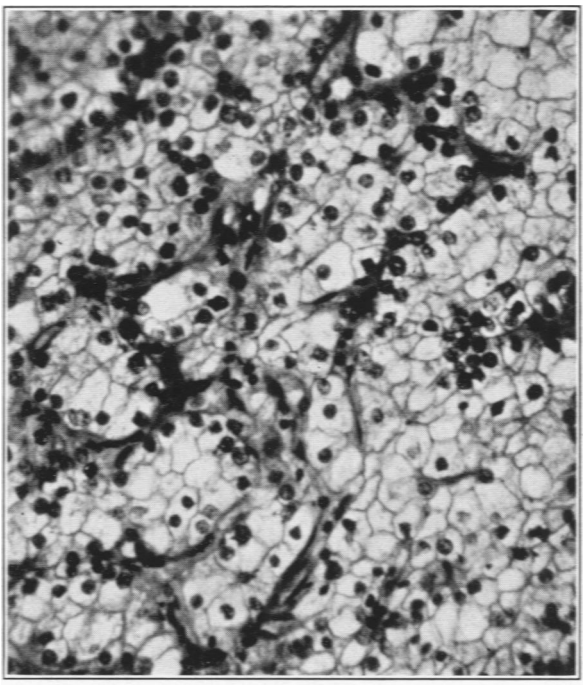

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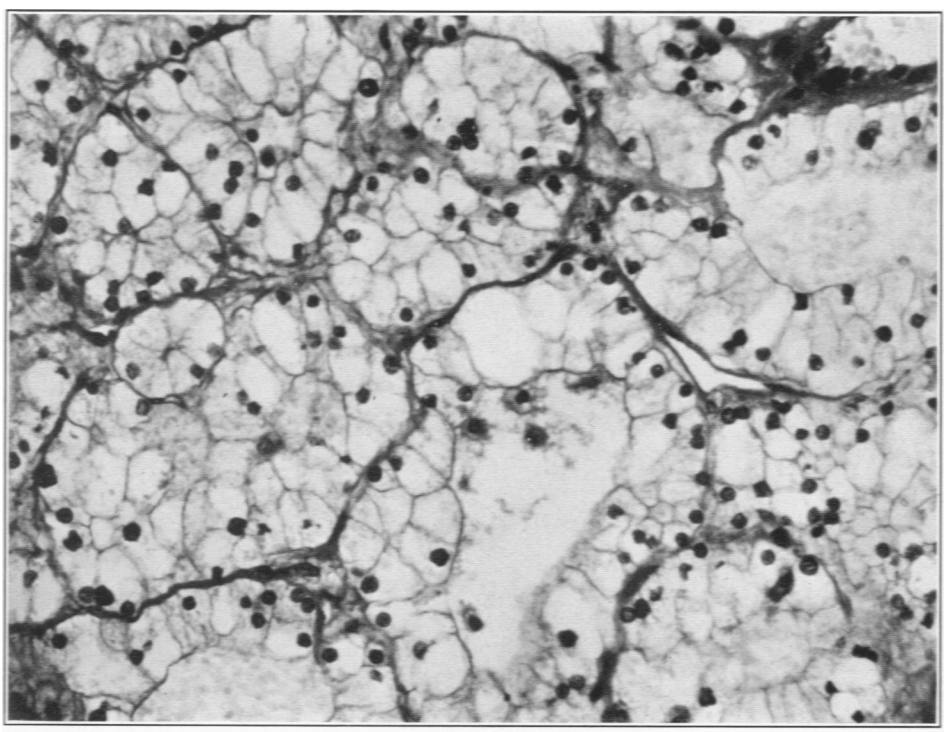

3

Castleman and Mallory

Parathyroid Hyperplasia in Renal Insufficiency

PLATE 90

FIG. 4. A drawing of the parathyroid glands in a case of parathyroid hyperplasia secondary to long-standing chronic renal disease.

FIGS. 5 and 6. A low power microphotograph of a section of one of the glands in Figure 4 showing the circumscribed encapsulated islands of cells. × 10.

FIG. 7. A higher power of several of the islands in Figure 5 showing the variation in the type and arrangement of the cells in the different islands. Note the islands of oxyphil cells on the left. × 150.

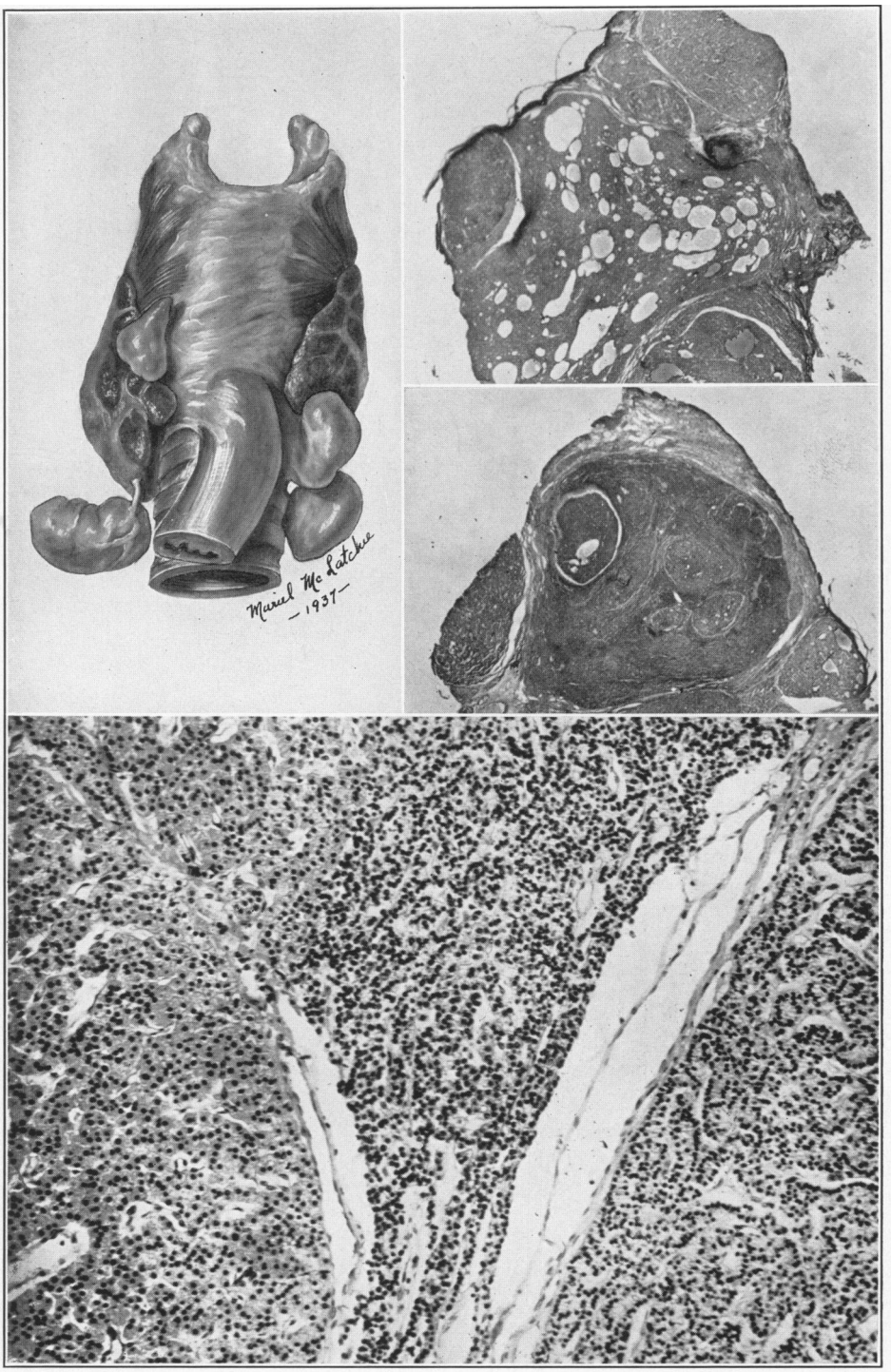

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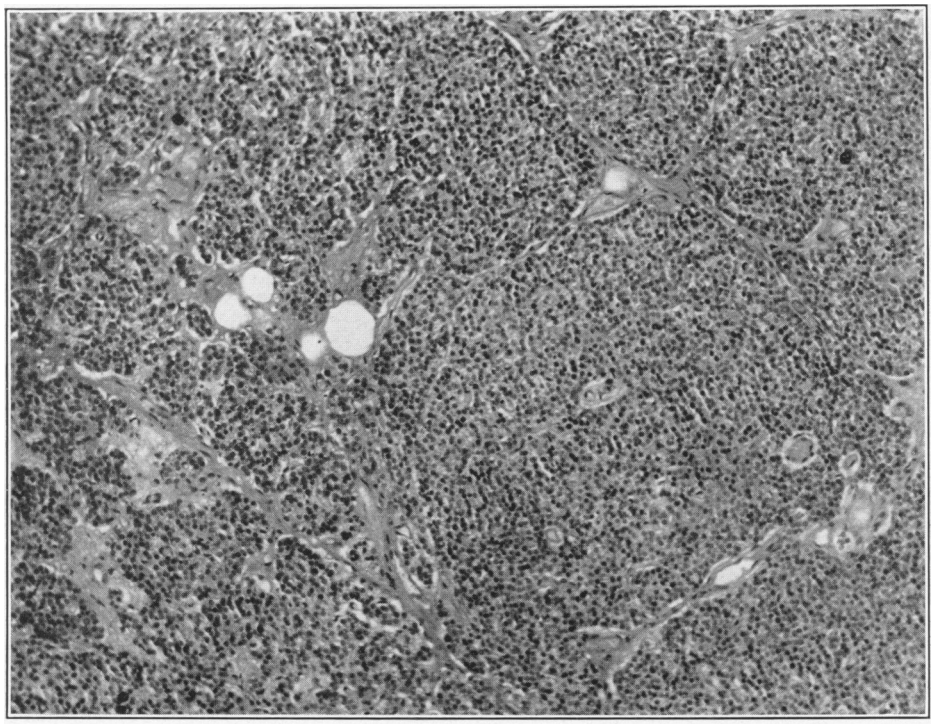
PLATE 91

FIG. 8. A microphotograph of a section of one of the glands seen in Figure 4. Note the cellular compactness, almost complete absence of fat, and the normal sized chief cells. In this gland the nodularity and island formation is relatively inconspicuous. × 150.

FIG. 9. A microphotograph of a section of vertebra from the same case showing well marked osteitis fibrosa. Note the large numbers of osteoclasts at the edge of the bone trabecula. × 500.



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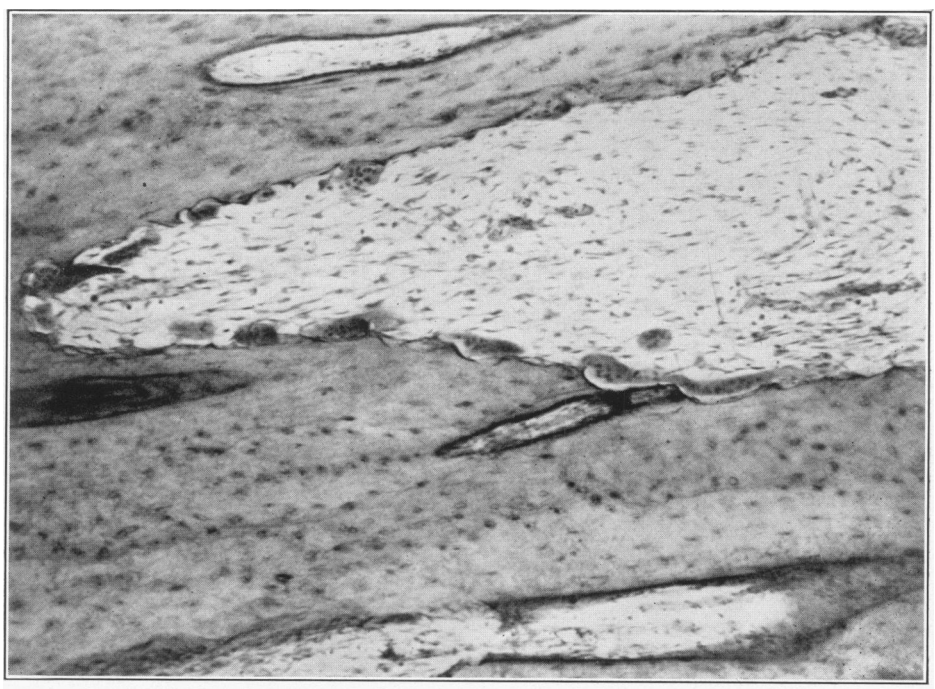

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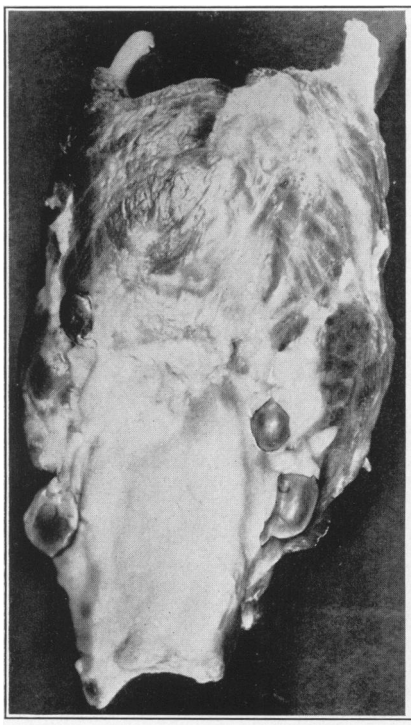
PLATE 92

FIG. 10. A photograph of the parathyroid glands in a case of chronic glomerular nephritis. Case No. 10 in Table 1. Note the enlargement and plumpness of the glands.

FIG. 11. A microphotograph of a section of one of the parathyroid glands in a case of chronic glomerular nephritis showing the solid sheets of cells without discernible columnar arrangement. × 500.

FIG. 12. A microphotograph of a section of one of the parathyroid glands in another case of chronic glomerular nephritis showing the slight vacuolization of the cytoplasm in some areas and the increased number of oxyphil cells. × 500.



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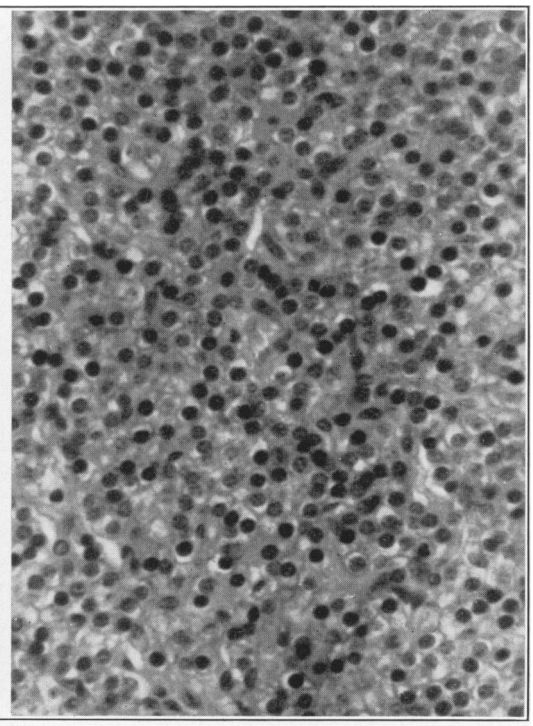

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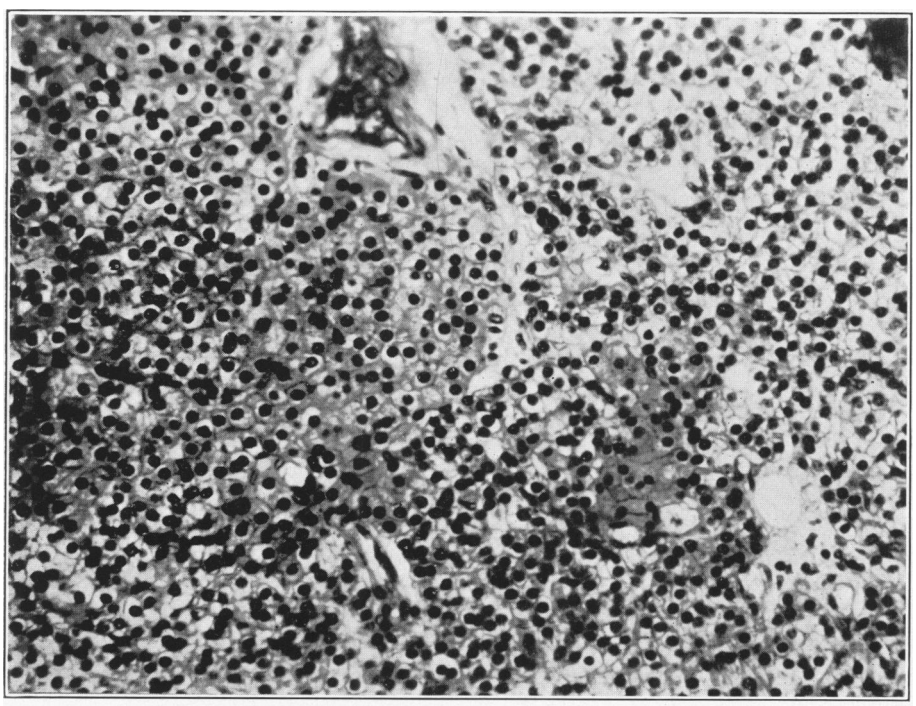

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