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# THE PATHOLOGY OF THE PARATHYROID GLAND IN HYPERPARATHYROIDISM *

## A STUDY OF 25 CASES

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## INTRODUCTION

De Santi [45] was the first to recognize a tumor of parathyroid origin in 1900, twenty years after the discovery of the glands in 1880 by Sandström.[124] During the next two decades scattered tumors were reported, usually from postmortem examinations. Although the association of these tumors with the clinical syndrome of von Recklinghausen's osteitis fibrosa generalisata had long been recognized, the cure of the disease following the surgical removal of an enlarged parathyroid gland by Mandl in 1925 [93] stimulated greatly increased interest in hyperparathyroidism. The rapidly growing list of case reports, numbering 160 at the time of writing, has added greatly to our knowledge of the condition. No one investigator, however, has hitherto had the opportunity to study more than a few cases, the largest series and the best histological studies to date emanating from Bergstrand with 6 cases,[20-24] and from Hunter and Turnbull with 5.[79, 80] The recognition by Albright and co-workers [3, 5] that systematic studies of the calcium and phosphorus metabolism in all cases of renal stones would unearth a significant proportion of cases of hyperparathyroidism, added to the already keen interest in the clinical syndrome dating from the work of Albright, Aub, Bauer and

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co-workers, [4, 6, 16, 118] Hannon *et al.*, [68, 97] has provided us with 25 cases for study. Within this group we have been able to find examples of nearly every type of the disease recorded in the literature, so that an effort at classification seems justified.

For purposes of orientation, since the classification, and still more the nomenclature, of the types of parathyroid cells is regrettably confused, a study of the normal glands seemed necessary. Although it provides little that can be considered new, we feel that our description of the normal will provide the reader with a base line from which he can more adequately evaluate our descriptions of the diseased glands. We therefore include it in brief form.

## The Normal Parathyroid Gland

In 1898 Welsh,[153] after examining the parathyroid glands from 40 human autopsies, published an accurate description of the histology of the normal gland, to which little of fundamental importance has been added. He recognized for the first time the "oxyphil" cell, which he distinguished clearly from the predominant "principal" or "chief" cell. The latter he separated into four subtypes, basing his classification partly on the morphology but more on their arrangement. He believed that the least specialized cell was what is now called the "water-clear" or "wasserhelle" cell, and that as the cell became more specialized it reached the stage of a true chief cell. The arrangement of both the oxyphil and chief cells varied from large continuous masses to anastomosing and then branching columns, and finally to cords a single cell wide. True acini were occasionally, but rarely, found and when present often contained colloid-like secretion.

During the past thirty years many anatomists have studied the normal histology of the parathyroid gland, describing various types of cells. One difficulty in comprehending this normal histology is the nomenclature. Von Verebély [147] describes chief, vacuolated, small and large oxyphil cells; Getzowa,[56] wasserhelle, rosarote and oxyphil cells; Hunter and Turnbull,[80] principal and pale and dark oxyphil cells; Erdheim,[50] a large pale and a dark oxyphil cell; Kurokawa,[85] clear and dark chief cells. This variation suggests that the cell types are not clearly differentiated and that transition forms are numerous.

In 1903 Erdheim [50] showed the presence of fat granules in the chief cells as well as in the stroma. Very little was seen in the oxyphil cells. The fat was not present at birth and began to appear after the third decade, gradually increasing with age. He emphasized the fact that the fat content was not dependent upon the nutrition of the individual, but only upon age.

Kurokawa [85] studied a larger series of about 815 glands removed from 240 autopsy cases at Keio University Medical College. His material ranged from a 7 month fetus to individuals 80 years of age and presents the most adequate survey yet available of the physiological limits of variation. His findings show that up to the age of puberty the cells are all clear chief cells containing glycogen but no fat. At this point these cells begin to decrease and the dark chief and oxyphil cells gradually appear. The dark chief cells contain fat but no glycogen. The oxyphils contain neither fat nor glycogen. Follicles and colloid appear at this time. The oxyphil cells increase with advancing age, occurring in masses and nodules after the age of 30 or 40 years. He found that after puberty there was no tendency for the interstitial connective or fatty tissues to increase, nor was there any atrophy of the gland.

In our study the parathyroid glands were removed from 150 routine autopsied cases. In the majority of these, four glands were found in their normal positions, though in occasional cases only three or even two could be demonstrated. In rare instances supernumerary and aberrant glands have been reported. Parathyroid tissue has been found in the thyroid, thymus, and in other regions of the anterior mediastinum.[28, 99] The glands in each case are usually the same size, though minor variations are not rare. On the average they measure 3–6 mm. in length, 2–4 mm. in width, and 0.5–2 mm. in thickness. They are usually embedded in fat tissue, from which they can be distinguished by their color, which varies from a dark reddish brown to a light tan.

Our material was for the most part fixed in Zenker's fluid, embedded in paraffin, cut at about 8 microns thickness, and stained with eosin and methylene blue. In numerous instances paraffin sections of formalin-fixed material stained with hematoxylin and eosin were also studied. Variations in fixation and staining technique were often found to alter the appearances of the cells significantly. The fat content was determined from frozen sections fixed in 10 per cent

formalin and stained in scharlach R. Preparations of alcohol-fixed material stained for glycogen with Best's carmine were made in about one-half of the cases. It was found that in all but a few cases the various glands from the same individual were practically identical in appearance. We have elected to recognize four major cell types and have been forced to admit the existence of transition types.

The normal chief or principal cell (Fig. 6) is polyhedral in shape, poorly outlined and measures 6–8 microns in diameter. Its nucleus is large, round, sharply demarcated by a basophilic outline, comprises more than half of the cell volume and measures 4–5 microns in diameter. The chromatin is usually abundant, often giving the nucleus a pyknotic appearance. The cytoplasm is usually very scant and faintly acidophilic. Often it is more or less retracted toward the cell margins, leaving an unstained halo of varying width about the nucleus. This is often spoken of as vacuolization, though it may represent merely an artefact of fixation and dehydration. Formalin fixation tends to exaggerate this appearance, and in frozen sections of unfixed tissue vacuolization is difficult to demonstrate even when paraffin sections show it in marked form. Cells showing this halo formation in moderate degree we have termed transition wasserhelle cells.

When the cytoplasm is apparently entirely absent, complete vacuolization, the cell is called a "water-clear" or "wasserhelle" cell. At this stage the cell is sharply outlined and is larger than the chief cell, measuring 10–15 microns in diameter. Its nucleus is about the same size as that of the chief cell, but is usually more hyperchromatic, more often pyknotic, and eccentrically located. These cells are seen only occasionally in the apparently normal gland and then in small groups. We have not observed them before puberty. Their presence in small clusters has sometimes been interpreted as focal hyperplasia. When the whole gland is composed of these cells, as in some cases of nephritis and hypertension, it is felt that hyperplasia is definite.

The pale oxyphil cell (Fig. 7) is polyhedral in shape, has a sharply demarcated cell margin and measures 11–14 microns in diameter. The nucleus is also about the same size as that of the chief cell, but not so hyperchromatic. The cytoplasm is uniformly reddish pink, finely granular and completely fills the cell. There is no vacuolization.

The dark oxyphil cell is larger than the chief cell but smaller than the pale oxyphil, and measures 8–10 microns in diameter. Its cell border is not sharp. The nucleus is small, 3–4 microns, and intensely pyknotic. The cytoplasm is dark red and homogeneous.

The distribution of these cells varies with age. Until puberty the gland is composed wholly of chief cells with a slight tendency to vacuolization (Fig. 1). We cannot subscribe to Kurokawa's[85] classification of them as wasserhelle cells. These cells contain a fair amount of glycogen but no fat, the latter appearing soon after puberty as very fine droplets. At puberty or soon afterward pale oxyphils gradually appear, at first singly and then in pairs. They increase in number with advancing age, forming large islands usually after 40 to 50 years of age (Fig. 3). These islands are sharply circumscribed but not encapsulated, and often continuous cords of parenchymal cells can be traced across the margin into the surrounding tissue. These cells do not contain fat or glycogen. Dark oxyphil cells occur singly and usually close to the stroma. They are not present before puberty, and occur usually when pale oxyphils are present. They likewise do not contain fat or glycogen.

Following puberty large fat cells appear in the stroma and increase in number until about 40 years of age (Fig. 2). The fat tissue remains fairly constant during middle age and does not increase with old age. In fact, in cases where the individual was over 80 years of age, in which oxyphil groups are numerous, it is somewhat diminished. It is interesting to note that when an adult gland is smaller than normal the decreased size is due to the absence or marked diminution of fat cells, whereas the parenchymal cell volume is about the same as in a normal sized fat-containing gland. These observations on the fat content do not wholly coincide with those of Erdheim.[50]

Cysts of varying sizes are observed in about one-half of the cases beyond puberty (Fig. 4). In 2 cases one of the glands was composed almost wholly of one large cyst similar to that described by Alagna.[2] These cysts are filled with granular and cellular débris or with a dark blue-staining, finely granular material which is often, though perhaps improperly, termed colloid.

In one case a small, circumscribed, apparently non-functioning adenoma 3–4 mm. in diameter with a distinct fibrous capsule was found in one of the glands. The cells of this tumor were classified as a transition stage between chief and pale oxyphil cells (Fig. 5).

## Cases of Hyperparathyroidism

The clinical and surgical aspects of many of these cases have already been reported elsewhere in detail and reference to them will be given with each description. Cases 1–17 are collected in a paper by Albright, Aub and Bauer.[4] The surgical features in the treatment of these cases have been reported by Churchill and Cope.[32, 33] The case numbers in the present series have been kept identical with those of the clinical studies.

With the gradual accumulation of material it became evident that one fundamental line of division could be drawn. One group of cases, the smaller one, was characterized by a diffuse, uniform alteration of all the parathyroid tissue in the body (Figs. 8–13). In the second group one gland, often only a part of it, rarely parts of two glands, were abnormal (Figs. 15–26), whereas the remaining parathyroid tissue was grossly and microscopically within the limits of normal variation. That the first group is to be regarded as hyperplastic, dependent on some external chemical, hormonal or nervous stimulation, seems obvious. That the second group falls within the accepted limits of neoplasia is a thesis we shall attempt to defend. The case reports which follow have been grouped according to this general classification and then further subdivided on purely morphological grounds of similarity of cell type and structure.

## Group A: Hyperplasia

Case 15 [8, 4, 32] (33–4840 and 34–796). *Clinical History:* A. P., a widow, 62 years of age, was first admitted in 1928 because of bilateral renal calculi. At this time two stones were removed from the right kidney pelvis, but in November, 1933, bilateral renal calculi were again found. The non-protein nitrogen was 32 mg. and the phenolsulphonephthalein excretion was only slightly impaired. The urine contained many white blood cells. A stone was removed from the left ureter. Serum calcium was 15 mg., phosphorus 2.2 mg., phosphatase 7.3 Bodansky units. X-rays of the skeleton were negative. On Dec. 19, 1933, at operation a parathyroid tumor was demonstrated below the right lobe of the thyroid and another on the left in a symmetrical position. Both were removed and the dissection was carried no further. Postoperatively the serum calcium at first fell, but soon began to rise. On Dec. 26, 1933, the serum calcium was 15.4 mg., the phosphorus 2.2 mg. On Feb. 28, 1934, a second operation was performed at which the left upper parathyroid was not demonstrated, but the right upper was found greatly enlarged and was resected, a portion about twice the size of a normal gland being left in place. In April, 1934, the serum calcium was 11.4 mg., the phosphorus 2.2 mg. When last seen, on June 30, 1934, the serum calcium was 13.78 mg., the phosphorus 2.75 mg.

*Gross Description:* The specimen removed from the region of the lower pole of the right lobe of the thyroid weighs 0.61 gm. and measures 1.5 by 1.2 by 0.5 cm. The gland is encapsulated, smooth surfaced and deep reddish brown in color. On one surface there is a curved shallow depression. The cut surface is homogeneously reddish brown. The specimen removed from the region of the lower pole of the left lobe of the thyroid weighs 0.51 gm. and measures 1.8 by 0.8 by 0.6 cm. It is slightly paler but otherwise the same as the other specimen.

The specimen removed 71 days later (34–786) from the region of the upper pole of the right lobe of the thyroid weighs approximately 10 gm. and measures 5 by 3 by 1.3 cm. Its surface is reddish brown, smooth and glistening, except where several small clear cysts averaging 0.5 cm. in diameter project from it. On section the surfaces are reddish brown, with cysts which yield a little clear straw-colored fluid.

*Microscopic Examination:* Both specimens removed at the first operation have the same microscopic appearance. The capsule is thin and no normal parathyroid tissue is found within or outside of it.

There is only one type of cell throughout, the wasserhelle cell (Fig. 9), which is polyhedral in shape, sharply demarcated by a thin eosinophilic membrane, and varies from 10 to 40 microns in diameter, averaging 15 to 20. Many of the cell boundaries are broken, with resultant fusion, similar to the fusion of alveoli in pulmonary emphysema. In contrast to the variability in the size of the cells the nuclei, though often multiple, are all approximately the same size, averaging about 8 microns 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. 11). 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. In fact one gland of this type was actually reported as a hypernephroma of the thyroid.[84]

The stroma is composed of thin, 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 pseudoglandular 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.

The cells in the specimen removed at the second operation are of the same type as those present in the other two glands. The same characteristic pattern is produced by the peripheral location of the nuclei, but there is more marked gland and cyst formation. These spaces vary in size from 0.1 to 5 mm. They are usually lined with a single layer of wasserhelle cells. Their lumina are filled with pink-staining granular débris and at times with desquamated lining cells and red blood cells (Figs. 8 and 9).

CASE 16[8, 4, 32] (34–634). *Clinical History:* T. F., a male, 26 years of age, entered on the urological service because of intermittent attacks of right renal colic for 15 months. Physical examination was negative. The non-protein nitrogen was normal. Serum calcium was 15.1 mg., phosphorus 1.8 mg. The urine showed finely granular casts of the hyperparathyroidism type (containing calcium phosphate).[7] X-rays of the skeleton were negative, but films of the urinary tract showed two small stones in the right ureter. These were removed and later, on Feb. 16, 1934, a parathyroid tumor below the right lower pole of the thyroid at the sternoclavicular junction was resected. Directly beneath this lay a second, much larger tumor, which came from the surface of the prevertebral fascia and the posterolateral aspect of the trachea and esophagus. This was also excised. The following day the serum calcium was 11.9, the phosphorus 2.6 mg. When last seen, on April 13, 1934, the serum calcium was 10.2, the phosphorus 2.3 mg.

*Gross Description:* The first gland is a well circumscribed, encapsulated, smooth surfaced, orange-brown ovoid mass weighing approximately 0.6 gm. and measuring 1.5 by 1 by 0.6 cm. The cut surface is uniformly yellowish brown.

The second gland is an encapsulated, smooth surfaced, ovoid soft tumor weighing approximately 15 gm. and measuring roughly 4.5 by 3.5 by 2.5 cm. Both poles are slightly pointed and narrowed. The surface is reddish brown. At one pole there is a small cyst 0.8 cm. in diameter filled with clear colorless fluid. The cut surface is homogeneously yellowish to reddish brown, soft and glistening.

*Microscopic Examination:* The microscopic picture of both of these tumors is identical. They are completely made up of large wasser-

helle cells of the same type as that seen in Case 15. There are no chief or oxyphil cells. No normal parathyroid tissue is present.

The cells in this case, as in Case 15, are in many places arranged in true gland formation. The characteristic pattern produced by the peripherally placed nuclei is much more pronounced than in Case 15 (Figs. 10 and 11).

CASE 17 [8, 4, 32] (34–600). *Clinical History:* J. M. M., a female, 55 years of age, entered on the urological service for intermittent attacks of renal colic for the past 14 months. Physical examination was negative. A stone demonstrated by X-ray in the right ureter was removed. The non-protein nitrogen was 31 mg. Serum calcium was 12.7 mg., phosphorus 2.4 mg., phosphatase 4.2 Bodansky units (normal). X-rays of the skeleton were negative. At operation on Feb. 14, 1934, all four glands were found in normal position and were enlarged. Three, and a portion of the fourth were removed. The following day the serum calcium was 10.9 mg., the phosphorus 2.2 mg. When last seen, on June 25, 1934, the serum calcium was 10.34 mg., the phosphorus 2.99 mg.

*Gross Description:* (*Left Upper*): A soft, reddish brown, slightly nodular, irregular, non-granular piece of tissue weighing 2 gm. and measuring approximately 2 by 2 by 1 cm. The specimen has been cut in several places. (At operation the recurrent laryngeal nerve had to be dissected free.)

(*Left Lower*): Weighs 0.6 gm., measures 1 by 0.8 by 0.4 cm.

(*Right Upper*): A small biopsy approximately 1 mm. in diameter.

(*Right Lower*): Weighs 0.8 gm., measures 1.8 by 1.2 by 0.4 cm.

The cut surface of all the specimens is homogeneously reddish brown.

*Microscopic Examination:* The microscopic picture of all sections is identical with Cases 15 and 16.

CASE 23 (34–2729). *Clinical History:* A. S., a male, 41 years of age. In August, 1932, the patient passed a renal stone. Three months later his physician removed three stones with the aid of a cystoscope. One month later he complained of a tight feeling in the left hip, soon followed by soreness in the hypogastrium and left lower quadrant. Cystoscopy was negative. He lost 35 pounds in weight. At the Massachusetts General Hospital in Feb., 1934, X-rays showed a cystic tumor of the left ilium and calcification in the lower pole of the left kidney. The bone lesion was resected and was diagnosed as an atypical chondrosarcoma. No changes in the least suggestive of osteitis fibrosa cystica were demonstrated. Examination of the urine showed a slight trace of albumin, 20–60 white blood cells, and occasional red blood cells. Bence-Jones protein was found on one occasion. The serum calcium was 13.1 mg., serum phosphorus 2.92 mg. After discharge the patient felt somewhat better for a while but soon the abdominal symptoms returned and he reentered for parathyroidectomy. The laboratory findings were essentially the same. On July 11, 1934, operation was performed.

The left upper, left lower, and right lower parathyroid glands were found enlarged and removed. A small biopsy was taken from an apparently normal sized right upper. Postoperatively the serum calcium went down slowly, reaching 10.18 mg. on the 10th day; the phosphorus was 3.4 mg. Three months later the corresponding figures were 11.96 mg. and 3.69 mg.

*Gross Description:* (*Right Lower*): a reddish brown, slightly flattened, smooth surfaced soft mass weighing 0.13 gm. and measuring 8 by 6 by 3 mm.

(*Right Upper*): A small biopsy 1 mm. in diameter.

(*Left Upper*): A multilobulated, reddish to yellowish brown, irregularly shaped, smooth surfaced mass weighing 2.18 gm. and measuring approximately 3 by 1.7 by 0.8 cm. The largest lobule measures 3 by 1 by 0.8 cm. and is more yellow than the rest of the specimen.

(*Left Lower*): A deep reddish brown, ovoid soft mass weighing 0.16 gm. and measuring 1.1 by 0.6 by 0.3 cm. The cut surfaces of all the specimens are homogeneously reddish brown.

*Microscopic Examination:* The cells are all of the large wasserhelle type, arranged in gland formation and showing the typical pattern seen in Cases 15, 16 and 17.

CASE 25 (34-4318). *Clinical History:* W. P., a male, 39 years of age, began in August, 1934, to have attacks of sharp pain in the right flank. The pain occurred suddenly at any time of the day or night and lasted 2 to 3 minutes. On October 1st he was awakened at night by an attack which persisted for several hours and which was finally relieved by morphia. During a 3 day period of observation at a local hospital he had three more similar attacks, all requiring morphia for relief. On Oct. 4, 1934, he was admitted to the Massachusetts General Hospital where a stone, demonstrated by a pyelogram, was removed from the right ureter. X-rays of the skeleton were negative. The serum calcium was 13.91 mg. per 100 cc., serum phosphorus 2.96, and phosphatase 3.67 units. At operation on October 27th the right upper parathyroid was found enlarged. A rush frozen section of a biopsy of this gland showed large wasserhelle cells typical of hyperplasia.* With this information the surgeon continued his search for the other glands and exposed all four. Both uppers were markedly enlarged and were resected. The lowers were much smaller. One of them was completely removed and three-quarters of the other was resected. On October 29th the serum calcium was 9.43 mg. per cent, serum phosphorus 1.34. There were no signs of tetany. The patient was discharged on Nov. 5, 1934.

*Gross Description:* (*Right Upper*): An irregular, slightly lobulated tumor weighing 4.96 gm. and measuring approximately 3.7 by 2 by

* In order to bring out the marked vacuolization of these wasserhelle cells it is advisable before freezing to fix the tissue by heating it to the boiling point in 10 per cent formalin.

1 cm. At one pole there is a long pseudopod-like projection 5 mm. in length and 3 mm. in diameter.

(*Left Upper*): Weighs 1.63 gm. and measures 1.7 by 1.7 by 0.6 cm. with a pseudopod-like tab 5 mm. in diameter.

(*Left Lower*): Weighs 0.11 gm. and measures roughly 4 mm. in diameter.

(*Right Lower*): Two small pieces weighing 0.10 gm.

The surfaces of all the specimens are smooth and reddish to yellowish brown. The cut surfaces are homogeneously pink to yellowish gray, moist and translucent.

*Microscopic Examination:* The microscopic picture of all sections is identical with Cases 15, 16, 17 and 23. A piece of thyroid removed at operation was histologically normal.

*Summary of Cases 15, 16, 17, 23 and 25 (Wassershelle, Generalized)*

The similarity of these 5 cases is at once apparent from an examination of the sections. The uniform, unusually large clear cells, the tendency to acinar arrangement and the basal orientation of the nuclei present a uniformity of appearance that is entirely lacking in the group of localized tumors to be described below. It differs also from the hyperplasia produced experimentally in rabbits by the injection of an extract of the anterior pituitary. In these experiments Hertz and Kranes [74] found enlarged chief cells with comparatively slight vacuolization and numerous mitoses.

The similarity to the clear cell renal adenocarcinoma is striking and in fact, as already reported in the text, has misled previous observers.[84]

In Cases 17, 23 and 25, histological specimens were obtained from all four glands and diffuse involvement of all the parathyroid tissue proved beyond doubt. In Case 15 only three glands could be demonstrated in two extremely thorough operative dissections. In Case 16 only two enlarged glands were demonstrated, but no search was made for the other glands at the time of operation and the patient has not returned to the clinic. However, the histological similarity to the other cases makes us feel that it should be classified with this group.

CASE 23A* (7119). *Clinical History:* R. N., a female, 25 years of age, entered the Maine General Hospital in April, 1933, complaining of weakness and fatigue. She had had polyuria and polydipsia all her life, with no recent change. Her teeth had all been loose for 7 years. She had had pain, weakness and numbness of the legs for the past 8 months. Examination showed a small mass 8 by 4 mm. in the middle of the right neck. The blood pressure was 158/78. Examination of the urine showed a fixed specific gravity around 1.005, 40–60 mg. of albumin, and 10–20 white blood cells. Examination of the blood showed a red cell count of 1,980,000, with a hemoglobin of 35 per cent. The white blood cell count was normal. The non-protein nitrogen of the blood was 150 mg. On her second admission in September, 1933, the laboratory examinations were about the same. X-rays of the skull, ribs and hands showed definite cysts, as well as calcification of the arteries and subcutaneous tissues. The serum calcium was 8 mg., serum phosphorus 9 mg. Although these blood studies appear paradoxical, they may be explained according to Albright by the marked renal damage. The phosphate retention secondarily causes a diminution in blood calcium. The patient died Nov. 6, 1933. Postmortem examination showed in addition to the parathyroid enlargement a marked chronic pyelonephritis and osteitis fibrosa. A clinical diagnosis of renal rickets could not be ruled out.

*Gross Description:* All the parathyroid glands except the right lower are enlarged. The left lower is ovoid in shape and measures 9 by 7 by 3 mm. The left upper is the largest and measures 17 by 8 by 5 mm. It contains on its posterior surface a circular nodular elevation 3 mm. in diameter. The right upper measures 10 by 8 by 4 mm. The glands are smooth surfaced, and in spite of having been previously fixed in formalin still retain a slight yellowish brown tint.

*Microscopic Examination:* All the glands, including the normal sized one, show essentially the same process in varying degrees, the most marked changes being in the largest gland. The capsules are thin and not remarkable. The predominating cell is the chief cell, which is normal in size, averaging 8 microns in diameter. The cell outline is poorly visualized. The nucleus is round, deeply pyknotic and hyperchromatic, sharply outlined, measures 5–6 microns in diameter, and fills more than two-thirds of the cell volume. The cytoplasm is acidophilic and coarsely granular. The cells themselves are, therefore, not hypertrophied.

The arrangement of the cells presents the most significant picture.

* In addition to the 24 surgical cases included in this study, we have had the opportunity to study the parathyroid glands removed at autopsy from a case at the Maine General Hospital. The findings are quite different from any of our own cases. The authors wish to thank Drs. John Hamel and Mortimer Warren for permission to report the pathology of this case.

In order not to break the series of cases from the Massachusetts General Hospital, this case is numbered 23A instead of 24.

Small groups of these cells, 10–20 in number, are surrounded by a thin connective tissue band often containing a very small capillary. The nuclei tend to be located at the bases of the cells and produce a definite pseudoglandular arrangement, although there is no lumen. Each group appears to be shrunken away from its connective tissue band, leaving a clear space about 6–9 microns in width. In many places, especially in the larger glands, acinar arrangement is much more marked, forming well circumscribed, papillary foci measuring up to 0.8 mm. in diameter (Figs. 12 and 13). These resemble closely the basophilism frequently observed in the pituitary. There is very little inter- or intracellular fat tissue.

Scattered throughout all sections, but more marked in the larger glands, are groups of typical, normal sized, pale oxyphil cells arranged in the same formation as the chief cells, even including the papillary form. There are no wasserhelle cells.

*Summary of Case 23A (Hyperplasia, Chief Cell Type)*

This patient showed three enlarged and one normal sized parathyroid gland all made up of normal sized chief and pale oxyphil cells arranged in pseudoglandular and papillary formations. There is very little fat tissue and no wasserhelle cells.

## Group B: Neoplasia

Case 6 [118, 68, 16, 97, 6, 5] (32–3985). *Clinical History:* C. M., a male, 35 years of age. The clinical history of Captain Martel has appeared so often in the literature that no attempt will be made to repeat it. The diagnosis made by Dr. Eugene DuBois in 1926 was the first clinical recognition of hyperparathyroidism in this country, and probably the second in the world. The coöperative attitude of the Captain made possible a series of metabolic studies that are unparalleled and have contributed enormously to our knowledge of the disease.

Operation was performed first by Dr. E. P. Richardson in 1926, and two normal parathyroid bodies were removed. An article describing the case has been widely misquoted as recording improvement following this operation, but any such tendency was temporary and may more fairly be attributed to the high calcium diet. As the disease progressed the renal damage became more marked and stones formed in the kidney pelves. The serum calcium averaged 15 mg., phosphorus 2.3 mg. At the seventh operation, by splitting the sternum a parathyroid tumor was found in the anterior mediastinum. Subtotal resection was performed. Severe tetany supervened, which was controlled with difficulty, owing to acidosis attributable to the renal damage. Six weeks after the removal of the parathyroid tumor a stone was passed into the left ureter, causing complete obstruction. With the patient in a dangerous balance between tetany and aci-

dosis and in the face of a markedly diminished renal function, a left ureterolithotomy was undertaken. Death occurred 26 hours later. Postmortem examination showed well marked osteitis fibrosa cystica with early evidence of healing, and marked renal calcinosis.

*Gross Description:* A smooth, round, hard nodule 2.5 cm. in diameter. On cutting through the nodule it is seen to have a calcified shell 1–2 mm. in thickness, the rest of the tumor being made up of soft, shiny, brownish material. The tumor has a soft fibrous pedicle.

*Microscopic Examination:* The tumor is made up of only one type of cell, the chief cell (Fig. 17), which measures about 8–11 microns and has a poorly demarcated, pinkish, polyhedral cell outline. The nucleus is large, filling about one-half of the cell body, is round, sharply demarcated, and contains a variable amount of chromatin. Many of the nuclei, especially of the smaller cells, are deeply basophilic and almost pyknotic. The cytoplasm is light pink, coarsely granular and in many places reticular. A large proportion of the cells has a vacuolated halo around the nucleus and in a few the vacuolation extends to the periphery. An occasional cell is multinucleated; there are no mitoses. The cells contain no fat. There are no typical wasserhelle or pale oxyphil cells and only an occasional dark oxyphil cell.

The cells are arranged in compact masses, columns, and in pseudoglands, though one section shows a few definite acini lined with chief cells and filled with pink-staining, homogeneous material. The vessels of the intervening stroma are more numerous, much larger and much more congested than those in the normal parathyroid. Scattered throughout the stroma are variable sized spaces without demonstrable lining measuring up to 1 mm. in diameter. Many of these are empty, but others contain colloid-like, pink-staining material or red blood cells, and occasionally a desquamated parathyroid cell. There are also small colloid droplets throughout the stroma.

CASE 7 (32–4132). *Clinical History:* M. R., a female, 36 years of age. In 1929 the patient developed dull pain in her arms and legs. In 1931, at another hospital where her bones were found to be decalcified and filled with cysts, a diagnosis of osteitis fibrosa cystica was made. Serum calcium was 14.1 mg., phosphorus 2.9 mg. On Oct. 19, 1931, a tumor, supposedly of parathyroid origin, was excised, but microscopic examination revealed thyroid tissue. A biopsy of the mandible, 6 months later, showed osteitis fibrosa cystica. On May 6, 1932, a right hemithyroidectomy was done and a tumor at the left lower pole was removed. Microscopic examination revealed thyroid and thymic tissue. In November, 1932, she

entered the Massachusetts General Hospital for the first time. The serum calcium was 12 mg., phosphorus 1.74 mg., phosphatase 16.9 units. X-ray confirmed marked decalcification and multiple fractures in the pubic bones. She had paralysis of the right vocal cord. On Nov. 15, 1932, after fruitless exploration of the neck, a tumor was found in the anterior mediastinum beneath the costal cartilage of the second rib at the border of the sternum. A subtotal resection was done. During convalescence the patient developed definite tetany, associated with a fall in serum calcium. On Nov. 29, 1932, the serum calcium was 5.16 mg., phosphorus 3.29 mg. When last seen, on May 17, 1934, the bones showed great improvement. The serum calcium was 8.39 mg., phosphorus 3.03 mg. The phosphatase was 5.08 units.

*Gross Description:* A pedunculated, brownish, lobulated, firm encapsulated tumor measuring 2.5 by 3 by 1 cm. The cut surface is brown and shows many firm lobules varying in size from 3–6 mm. in diameter.

*Microscopic Examination:* About the same as in the preceding case. Palisading of cells is very prominent. In many places the columns are so winding and the intervening vascular stroma so abundant that there is almost a papillary arrangement. Scattered throughout the stroma are numerous large mast cells.

CASE 9 (33–1226). *Clinical History:* J. R. C., a male, 33 years of age. In 1931 the patient gradually developed weakness, loss of weight, nocturia and pains in the legs noticeable when walking. In 1932 the pain in the legs was almost constant when upright. He became much weaker, lost 30 pounds in weight, and by January, 1933, was unable to work. A diagnosis of hyperparathyroidism was made at the Boston Dispensary, where X-rays were taken of his bones and calcification of the kidneys observed. A history of mild polyuria and polydipsia was elicited. In March, 1933, he entered the Massachusetts General Hospital, where X-rays showed marked generalized decalcification of the skeleton with cyst formation. There was a markedly depressed renal function, a low urine specific gravity and a secondary anemia. The serum calcium was 16.9 mg., serum phosphorus 3.02 mg. On April 4, 1933, at operation a tumor lateral and posterior to the lower portion of the left lobe of the thyroid was resected. The dissection was limited to the left side of the neck. Convalescence was characterized by prolonged and severe tetany. When last seen, on July 24, 1933, steady improvement in appetite and strength was noted. He had gained 30 pounds in weight, had much less pain on walking and less nocturia. The anemia had improved moderately although the renal function was the same. Calcium and phosphorus values were normal, but phosphatase was slightly elevated. X-rays showed no change in skeleton or kidneys.

*Gross Description:* An ovoid, yellowish pink, soft, encapsulated mass measuring 4 by 2.2 by 2 cm. and weighing 7 gm. The cut surface is soft, friable, mushy and yellowish gray.

*Microscopic Examination:* The capsule is slightly thick, in places

measuring almost 1 mm. It is composed of fibrous connective tissue with only a few cellular areas. One of these areas is close to the inner surface of the capsule and contains lymphocytes, red cells and deposits of hemosiderin.

The cells in this case are larger than those of the preceding 2 cases, measuring 11 to 14 microns in diameter. The nuclei measure 8–10 microns and are hyperchromatic, but no definite multinucleated cells or mitotic figures are seen.

### *Summary of Cases 6, 7 and 9 (Chief Cell Type Alone)*

These 3 cases are all composed of large, hyperchromatic chief cells arranged in pseudoglandular and columnar formation (Fig. 17). Cases 7 and 9 show well marked palisading. Neither the cells nor the stroma, which is vascular, contain any fat. There are no wasserhelle or pale oxyphil cells, and only an occasional dark oxyphil cell. Multinucleated cells are rare and no mitoses can be found.

CASE 1 (30–3056). *Clinical History:* M. J. S., a female, 46 years of age. In 1916, following a miscarriage, the patient noted a swelling in the right side of her neck. Between 1928 and 1930 she developed pain successively in the right arm, right thigh, left thigh and right forearm. A biopsy of the right ulna at the Worcester Memorial Hospital showed a giant cell tumor, for which she was given X-ray therapy. Numbness and pain in the legs increased. She entered the Massachusetts General Hospital where X-rays showed generalized osteitis fibrosa cystica. A secondary anemia was present. Serum calcium was 13.68 mg., phosphorus 2.58 mg. At operation a tumor was seen pushing the right lobe of the thyroid forward. Hemithyroidectomy with total resection of the tumor was performed. After 2 months the pains had diminished and appetite, strength and gait had improved, though anemia was still present. Calcium and phosphorus levels were normal. By the 8th postoperative month she had gained 40 pounds, all skeletal pain had ceased and constipation had disappeared. Her strength was better than since 1916. X-rays showed slight but definite improvement in the bones. Two and a half years later she felt very well except for occasional backache. The cysts remained unchanged by X-ray. The serum calcium was 9.38 mg., phosphorus 3. 41 mg., phosphatase 2.58 units.

*Gross Description:* A light brown, ovoid, moderately firm, encapsulated mass, measuring 6.5 by 5 by 3.5 cm., and weighing 53.2 gm. The cut surface is homogeneously pale, glistening and yellow brown.

*Microscopic Examination:* The major portion of all sections is made up of closely packed cells arranged in pseudoglandular, cord or strand-like columnar formations. The pseudoglandular areas are composed of irregular, rounded groups of cells, from five to fifty in each group. The columnar areas are usually two or three cells in

width, but are comparatively few in number as compared with the pseudo-alveolar.

The predominant cell is polyhedral in shape and varies in size from 5 to 20 microns (Fig. 18). Its cell outline is often indistinct, but in many places can be made out as a thin, slightly irregular pink line. The smaller cells have round and light staining nuclei; the larger, some of which are almost 20 microns in diameter, have large, irregular, and more hyperchromatic nuclei, sometimes reaching the size of four to six ordinary nuclei. Chromatin is abundant and usually a nucleolus can definitely be made out. For the most part the cytoplasm immediately surrounding the nucleus is absent, producing a halo from the periphery of which pinkish granules extend to the cell margins, though a fair proportion of the cells have a pink, finely granular cytoplasm which completely fills them. A small proportion of these cells has one or two small fat granules in its cytoplasm, but the majority of them contain no fat. Multinucleated cells are fairly numerous; some contain as many as seven nuclei. Although no mitoses are seen, the atypicality of the nuclei, as evidenced by the variation in their hyperchromatism and the frequency of multinucleated cells, strongly suggests a neoplastic rather than a hyperplastic process.

Single, dark oxyphil cells are present in small numbers. They are of normal size, about 8–10 microns in diameter, with a dark, deeply basophilic irregular nucleus surrounded by a deeply eosinophilic, finely granular cytoplasm. The nuclei are either small, about one-fifth the cell volume, or large, about three-fourths of the cell volume. These cells lie for the most part close to the interstitial stroma and are not found in groups. No wasserhelle cells are seen.

The stroma is composed of thin fibrous strands which pass around groups of cells, producing pseudo-alveoli or columns. A small proportion of the stroma is acellular, but most of it contains thin-walled capillaries lined by typical endothelial cells. In some areas larger vessels partially filled with blood are seen. There are practically no fat cells in the stroma.

Scattered throughout the tumor are irregularly shaped spaces varying in size from 50 to 200 microns. They have a connective tissue lining, are surrounded by masses of chief cells, and contain for the most part pink-staining, granular débris, occasionally a few red blood cells, but no colloid. Besides these there are also much larger,

irregular confluent spaces without any definite lining, which also contain pink-staining granular débris. These appear to be areas of localized edema of the stroma.

CASE 11 (33–2429 and 33–4429). *Clinical History:* M. T., a female, 53 years of age. From 1920 to 1923 she had pain in the legs and disturbance in gait. In 1929 an operation was performed on a giant cell tumor of the upper jaw. Later a second tumor in the nose was curetted. In 1930 she fractured the left forearm and left tibia by tripping on a rug. Abdominal pain led to an operation for replacement of the uterus. The severe pains in the legs continued and in 1931 a cystic tumor of the right tibia, discovered by X-ray, was curetted, but she remained completely invalided except for limited activity with crutches. In 1933 severe pain in the legs and lower back was associated with a spontaneous fracture of the neck of the right femur and a diagnosis of osteitis fibrosa cystica was made at the Cambridge City Hospital. She was transferred to the Huntington Hospital where the diagnosis was confirmed by Dr. J. C. Aub. X-rays showed extensive decalcification and cyst formation of the entire skeleton and calcium deposits in the kidney parenchyma. Her condition seemed critical, with respiratory distress, nausea and vomiting. The serum calcium was 13.7 mg., serum phosphorus 2.4 mg., the phosphatase elevated. Renal function was diminished. At operation at the Massachusetts General Hospital on June 24, 1933, a subtotal resection of parathyroid tumor found behind the left upper pole was performed. Approximately 1 gm. of parathyroid tissue was left. A nodular goiter was noted. A mild tetany developed, the calcium falling as low as 7.4 mg. A second fracture of the femur occurred when the traction apparatus was changed. In September, 1933, she was comfortable but the bones showed no evidence of increased density and the fractures failed to develop callus. The extreme decalcification of the skeleton was treated with a high calcium diet, vitamin C, viosterol and calcium glycerophosphate. The serum calcium rose to 11.53, the phosphorus was 3 mg. On Nov. 15, 1933, a second operation was done, with excision of the remainder of the parathyroid tumor. One week later the calcium was 8.47 mg., the phosphorus 3.12 mg. When last seen, on March 17, 1934, locomotion was much improved, and the fracture seemed solid.

*Gross Description:* A partially encapsulated, smooth brown nodule measuring 3 by 2 by 1 cm. and weighing 3.85 gm. Many vesicles are present on the surface. On section the center of the tumor is found to be composed of a calcified area roughly 5 mm. in diameter. The tumor tissue is homogeneously brown and firm.

A second piece of similar tissue measuring 2.1 by 1.1 by 0.8 cm. and weighing 1.2 gm. is also present.

*Microscopic Examination:* The capsule is moderately thickened and composed predominantly of acellular fibrous connective tissue. In a few areas there are some connective tissue cells and clumps of lymphocytes. The subcapsular vessels are markedly distended and congested.

This tumor contains three types of cells. The one that makes up the bulk of the tumor is the enlarged chief cell, similar to that seen in the group just described (Cases 6, 7 and 9). In sharp contrast to these cells there are intermingled with them large numbers of cells apparently in the same class as the chief cell, but tremendously enlarged, much more hyperchromatic, and similar to the giant type of cell described in the previous case. Under low power each field appears to be irregularly studded with them. These cells lie side by side and make up about one-third of the whole mass. They vary greatly in size, the smaller ones averaging 14–17 microns in diameter, the larger about 20 microns; many reach as high as 30 microns (Fig. 18).

The third type of cell in this specimen is similar to the slightly enlarged chief cell, except that its cytoplasm is homogeneously much more eosinophilic. These cells are arranged in large clumps and located only at the periphery. They are not the characteristic pale oxyphil cells but are merely a slight variation from the normal chief cell. No true pale oxyphil cells are seen.

The whole tumor has a well marked pseudoglandular arrangement. Although most of this formation is produced by columns and masses of cells surrounding and bordering capillaries and larger blood vessels, a large proportion is formed around unclassifiable spaces, many of which are filled with granular, blue-staining débris. In many places the cells bordering these spaces or blood vessels show definite palisading. Here the nuclei are located at the pole of the cell, away from the apparent glandular lumen. In places where only a single layer of cells surrounds a small capillary the nuclei are also at the pole of the cell, more distant from the capillary lumen. All types of cells share in this arrangement, although there is a tendency for the smaller ones to border the pseudogland or space.

The stroma consists of scanty strands of fibrous connective tissue, a small amount of fat, and vessels which are increased in number but not remarkably congested. No colloid is seen.

The remainder of the tumor (33–4429), removed at the second operation, is an irregular, orange-gray piece of tissue measuring 6 by 4 by 3 mm. Microscopically it is similar to the specimen removed at the subtotal resection. There is a large amount of scar tissue containing many foreign body giant cells distributed around and throughout the specimen, undoubtedly due to the trauma of the previous operation. The same three types of cells are found. The only

possible difference between the two specimens is the relatively increased vesiculation of the chief cells. The latter, however, have not reached the stage in which they can be called true wasserhelle cells.

An interesting incidental finding was the removal of a small piece of pinkish gray tissue measuring 1.5 by 0.7 by 0.4 cm., containing a small cyst-like structure 4–5 cm. in diameter. At operation this specimen, which was in the same field, was believed to be parathyroid. Microscopically it is a papillary cystadenoma, possibly carcinoma, probably arising in aberrant thyroid tissue.

*Summary of Cases I and II (Chief Cell Type with Giant Forms)*

The 2 cases in this group are similar to those in the first group (Fig. 18). They have in addition large numbers of giant forms of exceptionally hyperchromatic chief cells measuring up to 30 microns in diameter, many of which are multinucleated. There are no wasserhelle or pale oxyphil cells. The histological picture is strong presumptive evidence for a neoplastic condition.

CASE 3[5] (32–1304). *Clinical History:* C. S., a female, 13 years of age. In 1928 nocturia with enuresis and polyuria developed. She had always drunk large amounts of water. That same year she fractured the right forearm in two places following an injury of considerable violence. In 1930 a limp, at first attributed to fallen arches, was followed in 6 months by the appearance of a deformity of the left knee. This led to the removal of a cyst from the lower end of the femur, and in 1931 a similar deformity of the right knee developed. In March, 1932, X-rays of the skull, pelvis and vertebrae taken at the Massachusetts General Hospital were characteristic of hyperparathyroidism. Almost complete decalcification of the epiphyses, suggesting renal rickets, was interpreted as failure of calcification of growing cartilage. Serum calcium was 12.5 mg., phosphorus 4.7 mg., phosphatase 36 Bodansky units. Urinary calcium excretion was within normal limits, fecal calcium increased. Renal function was greatly reduced and non-protein nitrogen was elevated. On April 9, 1932, at operation a tumor between the trachea and esophagus on the right side was resected. The serum calcium fell to 10.36 mg. 6 hours later and reached 8.26 mg. in 22 hours, at which time she had moderate tetany. On May 9, 1932, the serum calcium was 5.67 mg., phosphorus 5 mg. When last seen, on May 14, 1933, she felt much stronger but was still subject to fatigue. There was no further polyuria or nocturia. X-ray films showed definite improvement.

*Gross Description:* A somewhat ovoid, smooth surfaced, moderately firm, light brown mass measuring 22 by 17 by 10 mm. and weighing 2.5 gm. The cut surface shows the same uniform light brown color.

*Microscopic Examination:* The capsule of the tumor is composed of thick fibrous collagenous connective tissue approximately 45 microns in thickness. Just beneath the capsule is a layer six to eight cells deep of normal parathyroid chief cells.

The predominant cell is an enlarged transition wasserhelle cell (Fig. 19). It varies from 10 to 15 microns in diameter, smaller than the typical wasserhelle cell and has a fairly sharply outlined cell membrane. The shape is for the most part polyhedral, although the cells are so closely packed that almost any kind of shape can be found. The nuclei are eccentrically placed, are large, 6–10 microns in diameter, round, with a sharp basophilic outline and filled with a large amount of chromatin. Most of the nuclei contain one large, deeply stained, eccentric nucleolus located close to the limiting membranes. In several there are as many as three definite nucleoli. The cytoplasm is almost completely vacuolated except for some pinkish, finely granular threads on the inner surface of the cell membrane. Fat granules are present in all the parenchymal cells.

Irregularly scattered through the section are focal groups of cells similar to, but distinguishable from, the predominant type. One of these foci, an area 1.5 mm. in diameter, consists of cells with a cytoplasm which is much clearer, cell outlines sharper, and nuclei slightly smaller and more basophilic. The cells in this area might easily be regarded as true water-clear cells. The other focal areas are similar to each other and consist of cells resembling the predominant cell, except that the cytoplasm is stained uniformly light pink. There are several of these groups throughout each section, averaging 0.1–0.15 mm. in size.

A few dark oxyphil cells are scattered singly through the rim of normal tissue and among the vacuolated cells nearby. No oxyphil cells are apparent in the central portion of the tumor. There are a few, very small, colloid-filled vacuoles among the cells just beneath the capsule, but none among the vacuolated cells.

The cells are arranged in pseudoglandular formation, groups of approximately five to twenty-five being closely packed and surrounded by fine connective tissue strands, some of which contain small capillaries. None of these groups of cells shows demonstrable lumina, so that they cannot be called true alveoli. Many of the smaller groups have a single celled layer arranged radially, suggesting rosette formation. The stroma is scant, although there is one

area in which a collection of large fat cells similar to those in the normal parathyroid is seen.

CASE 22 (34–2649). *Clinical History:* H. C. B., a female, 26 years of age, had an attack of left renal colic accompanied by hematuria in June, 1933, followed in the course of a year by three or four similar attacks. There were no other symptoms. She entered the Massachusetts General Hospital in June, 1934, where a left ureterolithotomy was performed. The serum calcium was 12 mg., serum phosphorus 2.65 mg. X-rays of the skeleton were negative. The urine showed a slight trace of albumin and many calcium phosphate casts. A renal function test showed 35 per cent excretion. On July 6, 1934, at operation the right lower parathyroid gland was found enlarged and was removed. A frozen section showed a tumor of the chief cell type. One normal gland was seen in the left upper region. Because of the frozen section diagnosis and the finding of one normal gland, a more extensive exploration was not done. When the patient was discharged the calcium was 10.06 mg., the phosphorus 3.64 mg.

*Gross Description:* An encapsulated, smooth surfaced, orange-brown soft mass weighing 0.16 gm. and measuring 1 by 0.7 by 0.4 cm.

*Microscopic Examination:* Around more than one-half of the tumor is a small rim of normal parathyroid tissue. The capsule of the tumor is composed of thick acellular connective tissue measuring approximately 0.5 mm. in thickness. The cells are all of the same type, transitional wasserhelle cells, similar to those seen in Case 3. They average 15–20 microns in diameter with nuclei 10–15 microns in diameter. Many of the cells are much larger and contain as many as seven nuclei. There are occasional small intracellular fat granules. Glycogen is present in all the cells but much more marked in the cells in the rim of normal tissue.

CASE 8 (32–4330). *Clinical History:* A. R., a female, 44 years of age, developed pain in the right hip in 1931. X-rays at the Huntington Hospital in March, 1932, showed an extensive destructive process in the right ilium. There was no appreciable decalcification of the skeleton. The serum calcium was 14 mg., the serum phosphorus 1.5 mg. A diagnosis of hyperparathyroidism was made by Dr. J. C. Aub and treatment with high calcium diet produced improvement of symptoms. X-rays taken at the Massachusetts General Hospital in November, 1932, showed a localized area of rarefaction and areas of increased density were seen in the right ilium and a stone in the right kidney pelvis. On Nov. 30, 1932, a tumor lying against the trachea on the right side posterior to the thyroid was excised. She had very slight postoperative tetany.

*Gross Description:* A slightly flattened, ovoid, brownish red, slightly lobulated, soft, encapsulated piece of tissue measuring 2 by 0.8 by 0.6 cm. The cut surface is glistening and brownish red.

*Microscopic Examination:* The capsule is thin, measuring approximately 30–35 microns, and is composed of acellular fibrous connective tissue. Except for a few places, the immediate subcapsular area is made up of enlarged chief cells, measuring 11–15 microns in diameter. These are usually several layers deep but in some places only a thin rim one to three cells deep.

The arrangement of these cells is variable; some are arranged in small compact masses, some in double or triple rows with a slight tendency to palisading, and others in definite alveolar formation. The connective tissue stroma is very vascular and the capillaries and vessels are congested with polymorphonuclears and red cells.

Toward the central portion of the tumor the cells become more vacuolated, almost reaching the stage of true wasserhelle cells. These transition wasserhelle cells comprise about one-fourth of the total volume.

The most striking feature of this case is the predominance of the oxyphil cells. They are scattered throughout the whole tumor but are more conspicuous near the periphery, occurring for the most part in large groups, although single and small groups of cells are seen everywhere. One group is consistent with the pale oxyphil cell. The other type of eosinophilic cell is more often single, larger, measuring 17–20 microns, polyhedral in shape, has a moderately clear outline and is more deeply stained. The nucleus is small, round, sharply demarcated, hyperchromatic, eccentrically placed and measures about 6–7 microns in diameter. The cytoplasm is deep pinkish red and filled with tiny darker red granules. These cells are similar to those found in the normal parathyroid gland — typical dark oxyphil cells — except that they are much larger. No mitoses are seen.

The stroma, which contains occasional mast cells, is composed of moderately cellular, highly vascular connective tissue, but very little fat. There are occasional collections of lymphocytes and also small, unidentified, pink-staining, granular ovoid masses which do not simulate colloid.

CASE 12 (33–3876). *Clinical History:* Y. D., a female, 51 years of age. In 1925 a left nephrectomy for calculi was performed. She continued to pass gravel intermittently for a number of years. In 1930 a stone was removed from the pelvis of the right kidney. X-ray 1 year later showed a duodenal ulcer. In June, 1933, X-ray showed a stone in the right kidney. The serum calcium was 11.78 mg., phosphorus 4.35 mg., phosphatase normal. A right nephrotomy was performed but she continued to have colicky abdominal pains. A stone was present

in the lower ureter when she was seen 2 months later. There were no bone symptoms. On Oct. 7, 1933, a small parathyroid tumor located just below the sternal notch was removed. A large thyroid adenoma palpated preoperatively was also removed. She developed moderate tetany when the serum calcium dropped on the second postoperative day to 9.03 mg. When last seen, in 1934, the serum calcium was 9.88 mg., phosphorus 3.01 mg. and she felt well.

*Gross Description:* A small, encapsulated, ovoid mass measuring 1 by 0.4 by 0.2 cm. The surface is pinkish gray and coarsely granular. The cut surface is homogeneously purplish red.

*Microscopic Examination:* The capsule is very thin and in places not evident. Scattered throughout are large areas of fresh hemorrhage apparently due to operative trauma. At one corner of the section there is a small semilunar-shaped rim of normal parathyroid chief cells. The remainder of the section is made up of the tumor.

The cells comprising the tumor are of two types, the transition chief cell and the wasserhelle cell. The former makes up most of the specimen and shows all gradations from the chief to the wasserhelle cell. The cytoplasm of most of the cells, however, is not so clear as that of the cells of the previous 2 cases (Cases 3 and 22). The true wasserhelle cells, many of which contain no demonstrable nucleus, are compactly grouped in circumscribed islands and are much larger than the transition wasserhelle cells. The tumor resembles certain portions of Case 8, in which foci of wasserhelle cells are prominent, but is more similar to Case 3.

CASE 14 (33-4618). *Clinical History:* M. R., a male, 52 years of age, had an attack of renal colic with slight hematuria in 1923. Similar attacks recurred in 1927 and 1929, and in April, 1933, he developed left costovertebral pain with chills and fever. One month later a left ureterolithotomy was done. The serum calcium was 15.09 mg., phosphorus 2.84 mg. X-rays in November, 1933, showed diffuse skeletal decalcification without cyst formation and small indefinite areas of calcification in the lower poles of both kidneys which were not present in May, 1933. On Nov. 29, 1933, a parathyroid tumor was removed from behind the right lobe of the thyroid just above the inferior thyroid artery. When last seen, on Dec. 4, 1933, the serum calcium was 10.51 mg., phosphorus 2.54 mg.

*Gross Description:* An elongated, encapsulated, kidney-bean-shaped tumor weighing 1.2 gm. and measuring 2.2 by 1.8 by 0.9 cm. The tumor is divided in about its midportion by a jagged horizontal line. The upper half is yellow, smooth surfaced, but definitely divided into cystic lobules 3-4 mm. in diameter. By transillumination small yellowish white specks are seen floating in a clear fluid. Aspiration shows that the cyst is multilocular and about 0.5 cc. of a

slightly viscid yellow fluid is withdrawn. The lower half of the tumor is solid reddish brown and smooth surfaced. The cut surface is brownish yellow and moist.

*Microscopic Examination:* Just beneath the rather thin capsule in one area is a small semilunar rim of normal parathyroid tissue. The remainder of the specimen is composed of transition wasserhelle and true wasserhelle cells. The appearance is similar to Case 12, except that in this case the wasserhelle cells are more numerous than the transition cells.

The large cyst and a few smaller cystic spaces are all lined by wasserhelle cells. Most of them are filled with granular débris; an occasional small one contains colloid.

### *Summary of Cases 3, 22, 8, 12 and 14 (Transition Wasserhelle, Chief Cell Type)*

The cells in these 5 cases are predominantly of the transition wasserhelle cell type — a stage between the chief and wasserhelle cell (Fig. 19). Cases 3, 8 and 22 are closer to the true wasserhelle cell, while Cases 12 and 14 are closer to the chief cell. Small fat granules are present in Cases 3, 8 and 22, but not in 12 and 14. The cells are all closely packed together and have no glandular arrangement. In 4 of the cases there is a rim of normal parathyroid tissue surrounding the tumor. Oxyphil cells are absent in all cases except Case 8. The latter has in addition slightly enlarged chief cells arranged in pseudoglandular formation.

CASE 10 (33–1943). *Clinical History:* M. S., a female, 54 years of age, developed at the age of 15 years severe "backstrain," which in light of subsequent events may have been a spontaneous fracture of a vertebra. Since then she had experienced frequency and incontinence of urine, culminating in 1932 in severe abdominal pain associated with increased disturbance of urination. There was loss of weight and appetite. Cystoscopy revealed a vesical calculus which was removed by cystotomy. Her renal function was poor. During convalescence routine blood studies showed that the serum calcium was 13.93 mg., serum phosphorus 2.98 mg., and phosphatase 3.4 units. The bones showed some decalcification by X-ray but no cystic areas. Relief from abdominal pain followed the operation, but increasing pain in the thighs made worse by walking led to a second hospital entry for further study of the hyperparathyroidism. On May 24, 1933, at operation a tumor lying adjacent to the left lower pole of the thyroid gland was removed. It was roughly twenty times larger than the normal inferior parathyroid which was seen on the right side. There was no tetany and convalescence was uneventful. On June 1, 1933, the serum calcium was 10.47 mg., serum phosphorus 3.85 mg. When last seen, on July 22, 1933, the patient had gained 12 pounds since operation and stated that she had not felt so well for years.

*Gross Description:* A pear-shaped, flattened, slightly firm, orange, encapsulated and pedunculated tumor 3 by 1.7 by 0.8 cm. The pedicle measures 1 by 1 by 0.4 cm. On one surface is a raised nodular area 3 mm. in diameter. The cut surface is uniformly yellowish brown and moist.

*Microscopic Examination:* The capsule is moderately thickened, measuring approximately 0.5 mm. It is composed of connective tissue strands between which are large numbers of congested vessels and many large fat cells.

This tumor is composed predominantly of two types of cells, similar to each other and both obviously related to the chief cell. There is, however, a definite dividing line between them.

The first type comprises a comparatively small proportion of the tumor and simulates the wasserhelle cell. The cell is polyhedral in shape with a fairly sharp pink outline and measures 10–14 microns in diameter. The nucleus is round, usually eccentric, sharply outlined, deeply basophilic, contains a moderate amount of chromatin and measures 7–9 microns in diameter. Except for a scanty, light pink, reticular cytoplasm, usually peripheral, most of the cell body is vacuolated. A few are completely vacuolated, but in general they have not reached the stage of true wasserhelle cells. No mitotic figures or multinucleated cells are seen. A small number of fat droplets are found in some of the cells. The stroma in this portion of the tumor is vascular. The capillaries are markedly congested with red cells and are so numerous that they often give the appearance of diffuse hemorrhage in between small groups or columns of cells. There are also larger endothelial-lined spaces, many of which are filled with a blue-staining, granular débris. No colloid or oxyphil cells are seen in this area.

The other and predominant part of the tumor is composed of slightly larger cells measuring up to 22 microns in diameter and averaging 15 (Fig. 20). Although these cells are not so sharply outlined as the others, many, neverthleless, have a sharp pink cell border. The nuclei, often multiple, are rounder, sharply outlined, for the most part centrally located, deeply basophilic and hyperchromatic and measure 8–10 microns in diameter. The most striking difference between the two cell types is in the cytoplasm, which shows almost no vacuolization and completely fills the cell body. There are no mitoses. The arrangement of the cells is also different. Here a large

proportion of the cells is arranged in well defined glands, averaging 65 microns in external diameter, with a lumen measuring about 22 microns in diameter. The single layer of lining cells is definitely cuboidal in character rather than polyhedral.

Many of the glands contain dark reddish pink, opaque, colloid-like masses, some completely filling the lumen, others only partially so. Some of the larger lumina show marginal vacuolization. Between these glands the stroma is scanty, but small endothelial-lined vessels, many filled with red cells and granular débris, are found. Occasional colloid droplets are seen in the connective tissue stroma. A small number of fat granules is seen in the cells, stroma and lumina. Although no true oxyphil cells are found, the predominant cell slightly suggests a transition stage to the oxyphil type.

CASE 19 (34–1526). *Clinical History:* T. G. Y., a male physician, 49 years of age, noted in January, 1932, the onset of malaise and muscle pains. In the course of 2 years he grew weaker and lost about 15 pounds in weight. Three months later he broke his clavicle during slight exertion. Slight nocturia had been noted for 5 years, but no gravel. Renal function test showed 30 per cent excretion. The serum calcium was 15.01 mg., phosphorus 2.61 mg., and phosphatase 14.1 units. X-ray showed changes in the bones characteristic of hyperparathyroidism and a questionable displacement of the esophagus to the left just above the sternal notch. On April 24, 1934, at operation a tumor arising close to the right inferior thyroid artery and extending backward and medially was subtotally resected, leaving a piece about twice the size of a normal parathyroid. The tumor had displaced the esophagus, as visualized in the X-ray film. The following day the serum calcium was 11.16 mg., phosphorus 1.25 mg., and phosphatase 13.2 units. When last seen, on June 15, 1934, he felt much better. The serum calcium was 8.04 mg., the phosphorus 3.82 mg.

*Gross Description:* A reddish brown, smooth surfaced, slightly lobulated and flattened, ovoid mass weighing 11.7 gm. and measuring 4 by 3 by 1.5 cm. Two small calcified areas 2–3 mm. in diameter project from the surface. One margin of the specimen is notched. The cut surface is homogeneously reddish brown and moist.

*Microscopic Examination:* A small rim of normal parathyroid tissue partially surrounds the tumor but is not separated from it by any definite fibrous tissue capsule.

The whole tumor is composed of a single type of cell which is polyhedral in shape, faintly outlined, and measures 11–16 microns in diameter. The cytoplasm is non-vacuolated, pinkish red, coarsely granular and completely fills all of the cell around the nucleus. The nucleus is round to ovoid, has a sharply demarcated basophilic out-

line, measures 6–8 microns in diameter and is usually eccentrically placed. The chromatin content is not very great and there are no mitoses. The cells contain no fat or glycogen. The appearance slightly resembles both the chief and pale oxyphil cell types, suggesting a transition stage.

The cells are closely packed in a manner similar to the arrangement of normal pale oxyphil cells but not, however, in islands or in palisade formation. The stroma contains no fat and is composed for the most part of large numbers of congested vessels, producing a pseudoglandular effect.

*Summary of Cases 10 and 19 (Transition Oxyphil, Chief Cell Type)*

These two tumors are composed predominantly of transition pale oxyphil cells, a stage between the chief and pale oxyphil cells (Fig. 20). They are arranged in glandular and pseudoglandular formation. No true oxyphil cells are present. One part of Case 10 has in addition a large area of transition wasserhelle cells.

CASE 4[6,5] (32–3542). *Clinical History:* N. B., a female, 41 years of age, developed in 1925, following her fifth pregnancy, weakness in the back and knees and pain in the legs on walking. These symptoms increased with her sixth pregnancy in 1927, during which treatment for fallen arches was instituted. The diagnosis of "bone disease" made by her physician when she fractured the right femur in 1928 became obvious the following year when fractures of the right clavicle and later the right humerus occurred. In 1930 she entered the Massachusetts General Hospital where X-rays showed marked decalcification of the skeleton, cyst formation, old pathological fractures and a renal calculus. The serum calcium was 14.25 mg., phosphorus 2.3 mg. On Sept. 12, 1930, operation was done. The search, which was limited to the immediate region of the thyroid gland, failed to reveal a tumor but two normal parathyroid bodies were removed. A high calcium diet with viosterol gave improvement in symptoms and X-ray showed an increased deposit of calcium in the skull. As evidence of hyperparathyroidism persisted she returned to the hospital. At a second operation on Sept. 28, 1932, a large tumor was found behind the esophagus on the surface of the deep cervical fascia and a subtotal resection performed. She had moderately severe tetany during convalescence. In December, 1932, the serum calcium was 8 mg., phosphorus 4 mg., and phosphatase 4.3 units. When last seen, on Aug. 8, 1933, her anemia had improved and she felt much better.

*Gross Description:* An elongated, encapsulated, nodular mass of firm brown tissue measuring 3 by 1.5 by 0.9 cm. The cut surface is homogeneously reddish brown.

*Microscopic Examination:* The predominant cell in this case is the slightly enlarged chief cell (see Cases 6, 7 and 9). These cells are dis-

tributed in several ways. The major portion of them form the lining of large numbers of glands and cystic spaces (Fig. 21), which show great variations in size, some as small as 45 microns and others as large as 1 mm. Several of these spaces are partially or completely filled with a light pink, finely granular material, but many contain homogeneous, pink-staining material which slightly suggests colloid, an impression reinforced by the presence of marginal vacuolization, such as is seen in the hyperplastic thyroid. However, the light color and the lack of real density is more in favor of coagulation of the finely granular material rather than colloid. This same material, somewhat more deeply stained, is also found throughout the stroma, in many places completely obliterating the interstitial tissues. Some of these spaces are wholly or partially filled with red cells and occasional chief parathyroid cells, which may be desquamated lining cells. The lining is usually a single cell layer, but there is a fair number with two and even three layered linings. A few contain fat droplets.

Between these glandular structures are large collections of the same cells. Connective tissue stroma often containing small capillaries separates these collections of cells into small groups, many of which are pseudoglandular, and are composed on the average of about twenty-five to fifty cells, with occasional small lumina. Small groups of these cells, 5–10, arranged in gland formation resemble fetal adenomas of the thyroid. In several places the acinar cells show some degree of papillary infolding. In other areas the cells are arranged in undulating columns of three to four rows, the intervening stroma being composed of a fine reticulum. A tendency to palisading is barely recognizable. No mitoses are seen.

Scattered throughout all sections are pale oxyphil cells arranged in large groups varying in size from 0.1 mm. to 7–8 mm. The cells are slightly larger and less uniform than the normal oxyphil cell, varying from 8 to 17 microns. The cell outlines are fairly distinct, reddish pink and round to polyhedral in shape, clearer than the chief cell, but much less sharp than the wasserhelle cell. The nucleus is ovoid, deeply basophilic, sharply demarcated, centrally placed, hyperchromatic and fills about one-quarter of the cell volume. An occasional cell is multinucleated. Because of the large quantity of chromatin it is often difficult to distinguish a definite nucleolus. The cytoplasm is pink and granular, and usually fills the cell, although occasionally there is a small halo around the nucleus. Occasional, single dark oxy-

phil cells, usually located near the stroma, are found interspersed among the pale oxyphil groups.

The stroma of the glandular portion is composed of relatively dense fibrous tissue and large collections of colloid-like material. In the compact and pseudoglandular areas it is much less fibrous, but vascular.

CASE 13 (33–4182). *Clinical History:* A male, 22 years of age, was perfectly well until October, 1932, when he developed painless hematuria. In March, 1933, an attack of right renal colic was followed by the passage of a stone 2 weeks later, but several more attacks, one of them on the left side, pointed to the presence of additional stones. Physical examination was negative. The serum calcium was 15.78 mg., phosphorus 2.8 mg., phosphatase 4 units. Following X-ray of the urinary tract a right nephrolithotomy was performed. On Oct. 28, 1933, at operation a small parathyroid tumor under the upper pole of the left lobe of the thyroid was removed. On the fifth postoperative day the serum calcium was 10 mg., phosphorus 2.32 mg. When last seen, on Dec. 1, 1933, he was well, did not tire at the end of the day as he had done before, and felt much stronger.

*Gross Description:* A moderately soft, smooth surfaced, well encapsulated, slightly flattened, round tumor mass measuring approximately 1.7 cm. in diameter and weighing 2.1 gm. The surface is slightly mottled pale to orange-brown. The cut surface is moist, yellow to pinkish brown. The periphery is light brown to yellow.

*Microscopic Examination:* The capsule is quite thick, measuring up to 2 mm. in places, and is composed of fibrous connective tissue in which are numerous, endothelial-lined empty spaces. In addition there are many more unlined spaces that are partially or completely filled with parathyroid chief or wasserhelle cells. A tempting though uncertain interpretation is to regard these spaces as capsular lymphatics containing tumor cells. In any event there is definite evidence of parathyroid cells within the capsule. In one place there is a large group of wasserhelle cells just beneath the capsule. One end of this group of wasserhelle cells definitely invades the capsule and divides it for some distance into two layers. In the outermost layers of the capsule, and in one area very close to the outer surface of the capsule, there are chief cells arranged in glandular formation. Although this picture strongly suggests capsular invasion, it can also be interpreted as a rim of normal parathyroid tissue which has been markedly compressed by the tumor.

Just beneath the capsule are small and large foci of closely packed wasserhelle cells. The nuclei lie in the corner of the cell that is closest

to the stroma, giving the whole area a pattern similar to that seen in Case 16, where the whole gland has the same appearance. Many of the cells have no nuclei.

Except for the above mentioned capsule and subcapsular areas the specimen is composed of chief cells arranged in marked cystic and glandular formation, similar in parts to the glandular section of Case 4 (Figs. 22 and 23). There are no oxyphil cells. The cells are arranged in fairly compact masses and surround large numbers of cystic, irregular, papillary spaces, varying from 0.1 to 3 mm. in diameter. In many places these cystic spaces are lined by only a single layer of chief cells, but usually they are surrounded by the compact layers of the parenchymal chief cells. Some of these spaces are empty; many contain pink-staining granular débris; others are filled with red cells. The stroma is fairly abundant, contains many small vessels and no fat cells.

CASE 18 (34–1387). *Clinical History:* J. F., a female, 58 years of age. In 1924, 10 years before admission, the patient fractured her left femur after severe trauma, and had remained lame. In 1933 she fainted while at stool, fell, and broke the left femur again and also the left humerus. There were no genito-urinary symptoms. X-rays showed bone decalcification. The serum calcium was 11.36 mg., phosphorus 2.53 mg., and phosphatase 5.75 units. On April 13, 1934, at operation a tumor lying on the terminal divisions of the right inferior thyroid artery was resected. When last seen, on April 23, 1934, the calcium was 9.31 mg., phosphorus 3.32.

*Gross Description:* A flattened, almond-shaped, smooth surfaced mass 1.2 by 0.8 cm. by 0.4 cm. At one pole there is a semilunar area approximately 3 by 2 by 1 mm. which is yellowish brown and which is taken to be normal parathyroid tissue. The remainder of the specimen is dark purplish red and soft. This was thought to be tumor, although a hematoma in a normal gland could not be ruled out.

*Microscopic Examination:* A rim of normal parathyroid tissue surrounds the tumor. The dark purplish area observed grossly is a very vascular tumor. All the vascular channels, both small and large, are dilated and congested, producing a pseudo-acinar and in places papillary effect. The latter is further emphasized by the presence of numerous, irregularly shaped cystic spaces into which villus-like groups of cells project. Many of these spaces are empty, others filled with granular débris or red cells, and a few with colloid.

The cells are all of the chief and transition wasserhelle variety. No true wasserhelle cells are seen. Pale and dark oxyphil cells are absent. There are occasional intracellular fat droplets, but no intercellular fat globules such as are seen in the rim of normal parathyroid.

*Summary of Cases 4, 13 and 18 (Glandular Cystic, Chief Cell Type)*

These 3 cases are composed predominantly of slightly enlarged chief cells lining and surrounding numerous cystic and glandular spaces (Figs. 21, 22 and 23). This process is more prominent in Cases 4 and 13. Case 4 has in addition many islands of pale oxyphil cells. A rim of normal parathyroid tissue is present in Cases 13 and 18.

CASE 2 (32–157). *Clinical History:* M. L., a female, 60 years of age, experienced in 1928 a pain in the back which was intensified by motion, and followed by swelling and pain in the shoulder, knee and ankles. In February, 1931, a diagnosis of mild hypertrophic arthritis and osteomalacia was made. Serum calcium was 10.4 mg., phosphorus 3.6 mg. Treatment with a high calcium diet and viosterol resulted in considerable relief of symptoms, though the pain in the ankles and the aching in the knee continued and she was still subject to fatigue and inability to work. The diagnosis was temporarily changed to osteoporosis because of the consistently low phosphorus. Careful studies showed slight but constant elevation of serum calcium and low phosphorus, and a diagnosis of hyperparathyroidism was made. At operation, on Jan. 14, 1932, the right lower parathyroid body appeared considerably larger than normal and was removed. Convalescence was uneventful, without tetany. Serum calcium was 10.65 mg., phosphorus 3.68 mg. When last seen, on May 27, 1933, she was optimistic, felt much better and was working.

*Gross Description:* A smooth surfaced, moderately firm, ovoid, brownish mass measuring 10 by 5 by 4 mm.

*Microscopic Examination:* A section is taken through the whole mass. Under low power one sees a well circumscribed, encapsulated tumor, on one side of which is a peripheral zone of normal parathyroid tissue (Fig. 15). The tumor makes up about five-sixths of the specimen.

The capsule of the tumor is composed of a thin layer of acellular fibrous tissue. At one end of the section is a large, recent hemorrhagic area between the capsule of the tumor and the surrounding normal parathyroid tissue. In one place the hemorrhage has apparently broken through the capsule and is seen in the tumor.

The predominant cell is the typical wasserhelle cell (Fig. 16), measuring between 17 and 22 microns. The shape is usually poly-

hedral, but in the closely packed areas may be variable. The cell outline is a thin, sharp pink line, much more conspicuous than that of the normal parathyroid chief cells. The nucleus is eccentrically placed in one corner of the cell, is also sharply outlined and is deeply basophilic. It is round in shape, either clear or opaque, and measures about 8 microns. The nucleolus is just to one side of the center, is fairly conspicuous, and is surrounded by a large number of chromatin granules. Occasionally no nucleus is seen.

The cells are completely vacuolated, entirely lacking in demonstrable cytoplasm but contain moderate numbers of fat droplets. They can be regarded only as wasserhelle cells. In general the cells show no definite arrangement, although a single gland is noted. No mitotic figures are found.

In each section there are two to three large collections of cells which simulate the wasserhelle cells. They are about the same size and have a similar nucleus. The cell outline, however, is poorly defined and the cytoplasm is composed of a fine, reticular-like, pink cytoplasm in which are scattered, coarse, more brightly pink-stained granules. They have not the homogeneous cytoplasm of a true pale oxyphil cell, but may be a transition form (see Cases 10 and 19).

No oxyphil cells are found in the tumor, although they are present in fair numbers in the surrounding normal parathyroid tissue.

The stroma is scant and made up almost solely of fine capillaries and occasional small, vacuolated spaces, 11–15 microns in diameter, which contain homogeneous, pink-staining, colloid-like masses. One portion of the tumor contains a number of large fat cells similar to those seen in the surrounding normal parathyroid tissue.

*Summary of Case 2 (Neoplasia: Wasserhelle, Generalized)*

An encapsulated tumor composed predominantly of wasserhelle cells, scattered among which are a few large collections of probable transitional oxyphil cells. There are no mitoses or multinucleated cells. There is a rim of normal parathyroid around a portion of the tumor (Figs. 15 and 16).

CASE 5 (32–3594). *Clinical History:* R. T., a female, 55 years of age. In 1922 the patient developed attacks of severe pain in the right flank, radiating to the epigastrium, for which the gall-bladder was removed in 1927. The attacks not only were not relieved but became more severe. She was easily fatigued. In September, 1932, at the Massachusetts General Hospital a stone, shown by

X-ray in the pelvis of the right kidney, was removed by pyelotomy. Routine blood chemistry studies showed the serum calcium to be 13.2 mg., phosphorus 2.78 mg., phosphatase 5 units. On Oct. 3, 1932, a parathyroid tumor below the left lower pole of the thyroid was resected. A mild tetany was present postoperatively. When last seen, on Dec. 9, 1932, the serum calcium was 10.34 mg., phosphorus 3.71.

*Gross Description:* A slightly firm, reddish, and in places orange, slightly ecchymotic, encapsulated tumor measuring 1.5 by 1 by 1 cm. The cut surface is homogeneous, smooth, glistening and orange to reddish gray.

*Microscopic Examination:* The capsule is thin. Under low power one can see fairly large circumscribed masses of wasserhelle cells scattered at intervals through the tumor, which is elsewhere composed of chief cells (Fig. 24). These masses vary in size from 0.1 to 1.5 mm. in diameter. The subcapsular portion contains large collections of dark oxyphil cells.

The wasserhelle cells probably make up more than half the tumor. They are polyhedral, closely packed and measure 11–20 microns in diameter (Fig. 24). Their cell outlines are thicker than normal, reddish pink and ragged, but are easily seen because of the vacuolated cytoplasm. The nucleus is large, measuring 8–11 microns, eccentrically placed, round, sharply circumscribed, deeply basophilic, and so packed with chromatin that in many instances the nucleolus cannot be made out. The cytoplasm for the most part is completely vacuolated. A few cells contain pink-staining, coarsely granular débris, others lighter but brighter pink, homogeneous clear droplets 3–5 microns in diameter. No fat droplets are seen. There are no mitoses. Scattered among these cells are a few that have a light pink granular cytoplasm. These may well be transitions between the chief cell and the fully developed wasserhelle cell. No true oxyphil cells are found in the wasserhelle groups. The stroma between these wasserhelle cells is scant, but where it is present definite endothelial-lined vessels containing red blood cells are found. A few of the colloid-like droplets are also found in the stroma. Scattered throughout are irregularly shaped small spaces, which vary from 15 to 90 microns, most of them empty, but some containing pink-staining débris and others red blood cells.

Around the wasserhelle groups are slightly enlarged chief cells arranged for the most part in compact masses, in a few areas toward

the periphery in well formed glands with walls one to three cells deep, many of which are filled with red cells. Near the periphery, where the chief cells predominate, the stroma is markedly congested and contains large globules of fat.

Groups of typical, normal dark oxyphil cells are found close to the periphery, while single ones are distributed throughout the gland, except among the wasserhelle cells.

*Summary of Case 5 (Neoplasia: Wasserhelle, Focal)*

An encapsulated tumor composed of both chief and wasserhelle cells (Fig. 24). The latter are arranged in circumscribed masses making up more than half the tumor; the former are smaller and arranged in compact masses and in a few places in glands. There is very little fat in either type of cell.

CASE 20 (34–2321). *Clinical History:* N. M. K., a female, 36 years of age, in 1928 had her first attack of renal colic followed by a similar attack 3 months later. In 1930 stones were removed from the left kidney and right ureter but she continued to have attacks of renal colic. In 1933 she was delivered of a healthy full term child, following which she passed many small stones and developed polydipsia. There was no history of bone or joint pains or loss of weight. She entered the Massachusetts General Hospital in May, 1934. The urine was loaded with white and red blood cells, and had a fixed low specific gravity. The phenolsulphonephthalein test showed 40 per cent excretion. The serum calcium was 12.16 mg., phosphorus 3.27 mg. and the phosphatase 6–8 units. On June 13, 1934, at operation both upper parathyroid glands were found enlarged and were removed; both lowers were normal in size and a biopsy of each was taken. Serum calcium and phosphorus taken 7 hours postoperatively were 9.56 mg. and 2 mg. respectively. Mild tetany developed on the second postoperative day. When discharged, on June 25, 1934, the serum calcium was 10.62 mg., the serum phosphorus 4.52 mg.

*Gross Description: (Right Upper):* A yellowish brown, with reddish mottling, encapsulated mass 1.3 by 0.7 by 0.3 cm., weighing 0.28 gm.

*(Left Upper):* A light brown, flattened, round encapsulated mass measuring 1 by 0.8 by 0.3 cm. and weighing 0.3 gm. The biopsies from the lower glands are light brown in color and measure about 1 mm. in diameter.

*Microscopic Examination: (Right Upper):* The thin capsule is composed of acellular fibrous connective tissue and no rim of normal parathyroid tissue can be demonstrated around the tumor. The blood vessels are markedly congested and in addition there are many

large extravascular collections of red blood cells. The predominant cell throughout the tumor is a typical enlarged chief cell with the usual ill-defined cell outline and large hyperchromatic round nucleus, similar to that seen in Case 6. The cells average 10 microns in diameter, the nuclei 7 microns. The arrangement is protean. There are compact masses, anastomosing cords running between dilated capillaries of sinusoidal appearance, and large areas of gland formation. Many of the glands are lined with chief cells resembling the bulk of the tumor. Other glands, however, are of a totally different appearance, resembling none that we have seen in any of our other cases.* The lining cells here do not resemble chief cells. They are columnar in shape with basal nuclei and a rather localized area of vacuolization which does not surround the nucleus but always lies in the opposite pole of the cell toward the lumen of the gland. The appearance closely simulates the duct of a mucous gland lined by goblet cells. Both types of glands are filled with red cells (Fig. 26). Wasserhelle cells are completely, and pale and dark oxyphil cells practically, absent. In an occasional area normal pale oxyphil cells surround some of the glands.

The stroma is for the most part scant, with wide and thin-walled capillaries and many foci of hemorrhage, but in a few places several isolated cells are surrounded by irregular areas of almost acellular, richly collagenous fibrous tissue. There are no intercellular fat droplets. A small amount of colloid is present.

(*Left Upper*): This gland is quite different from the right upper (Figs. 25 and 26). In this instance a rim of normal parathyroid tissue containing many large fat cells in its stroma surrounds the tumor and is separated from it by a fairly thick connective tissue capsule. The cells are all of the same type — the transitional wasserhelle cell. There are a few intracellular fat droplets. Glycogen is present in normal amounts. Except for the absence of true wasserhelle cells, this specimen is similar to Case 12. There are no pale oxyphil cells and only an occasional normal dark oxyphil cell. All the cells are massed compactly together with little stroma. In a few places near the periphery there is a slight tendency to pseudo-alveolar arrangement and a slight resemblance to the pattern observed in the hyperplastic group.

* Case 24 in the Massachusetts General Hospital series, which is not reported in this paper because operation was performed after the paper was submitted, shows a single adenoma with this same histological picture.

The biopsies from the two lower glands show normal parathyroid tissue.

CASE 21 (34–2362). *Clinical History:* E. T., a female, 35 years of age, had an attack of left renal colic followed by the passage of a stone in November, 1933. Three months later several stones were removed at a local hospital. X-rays of the skeleton were normal. Following operation she felt well except for easy fatiguability and occasional low backache. She entered the Massachusetts General Hospital in June, 1934. Physical examination was negative. A renal function test showed 65 per cent excretion in 2 hours. The serum calcium was 11.92 mg., serum phosphorus 2.86 mg. On June 16, 1934, at operation the right lower parathyroid was found enlarged and was resected. The right upper was about the same size and a small biopsy of it was taken. No parathyroid tissue was found on the left side, even after the left lobe of the thyroid had been removed and carefully examined. On June 17th the serum calcium was 8.6 mg., phosphorus 3 mg. On the second postoperative day she developed mild tetany which lasted only a few days. When discharged, on June 26, 1934, the serum calcium was 10.34 mg., phosphorus 2.9 mg. A stone was still present in one kidney.

*Gross Description:* (*Right Lower*): A moderately firm, yellowish brown encapsulated mass 1 by 0.6 by 0.3 cm. The cut surface is uniformly yellowish brown. (*Right Upper*): A small biopsy approximately 2 mm. in diameter.

*Microscopic Examination:* (*Right Lower*): Around one edge of the tumor is a small rim of normal parathyroid tissue composed of chief cells and several large fat globules. The capsule of the tumor is thin. The tumor is composed for the most part of two types of cells, chief and pale oxyphil, with a slight predominance of the oxyphils. The chief cells of the tumor measure about 10–12 microns in diameter, the nuclei 8–10 microns; those in the rim of normal tissue measure 7–8 microns with nuclei of 5–6 microns. The cytoplasm is only slightly vacuolated and contains an occasional tiny fat granule and a normal amount of glycogen. There are no extracellular fat globules. The arrangement of the tumor cells is pseudoglandular. In many places, however, pale oxyphil cells are adjacent to chief cells, but almost all the latter are true chief cells and not in transitional stages to pale oxyphils. Glycogen is present in normal amounts. In addition to the scattered, single, pale oxyphil cells many of them are arranged in large islands. This finding is unusual in a person 35 years of age.

The biopsy of the upper gland shows a similar picture.

*Summary of Cases 20 and 21 (Neoplasia: Multiple)*

In each of the 2 cases two tumors were found composed predominantly of chief cells. In Case 20 one is definitely glandular; the

other is non-glandular, made up wholly of the transition wasserhelle cell and has a rim of normal parathyroid tissue. In Case 21 both tumors have the same appearance and contain many pale oxyphil cells, both single and in large groups.

## Review of the Literature

One hundred and sixty cases of probable hyperparathyroidism have been collected from the literature and the significant data tabulated (Table VI, see page 50). We have attempted to include all tumors and tumor-like enlargements of the parathyroid glands but have excluded from the series cases of osteomalacia, rickets, and primary nephritis in which slight secondary parathyroid hyperplasia is frequent. Rigid proof of hyperparathyroidism is often lacking, but in cases of marked parathyroid enlargement the burden of proof rests on the disclaimer.

Many of the case reports are regrettably incomplete, either in the clinical or in the anatomical details, and this considerably limits the value of the table. Knowledge of the syndrome of hyperparathyroidism has developed slowly and although the association of a parathyroid tumor with bone lesions was reported as early as 1903 by Askanazy,[10] it was not until 1913 that the combination began to be noted by a significant proportion of writers on the subject. Even at the present time the association with renal stones is still largely unrecognized and the experience in our clinic strongly indicates that more attention devoted to this phase of the disease will greatly increase the proportion of cases in which renal calculi are reported.

### *Statistical Data*

### *Age*

Including our series the ages are stated in 176 cases.

Table I

*Distribution per Decade*

| Age in years | 0–9 | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 |
|---|---|---|---|---|---|---|---|---|---|
| Total cases .... | 0 | 11 | 28 | 29 | 44 | 43 | 12 | 8 | 1 |
| Adenomas ..... | 0 | 10 | 25 | 27 | 37 | 38 | 11 | 5 | 1 |
| Hyperplasias ... | 0 | 1 | 3 | 2 | 7 | 5 | 1 | 3 | 0 |

The highest incidence of hyperparathyroidism is between 40 and 60 years of age. There is no significant difference in this regard between the group of localized tumors and the group of diffuse hyperplasias. Although the youngest case recorded is 13 years of age (our Case 3), the symptoms in this patient were clearly of at least 4 years duration, so that the occurrence of the disease in the first decade is to be expected in rare instances.

### *Sex*

Sex is reported in 174 cases.

TABLE II

*Sex Incidence*

| | Females | Males |
|---|---|---|
| Total | 122 | 52 |
| Adenomas | 108 | 45 |
| Hyperplasias | 14 | 7 |

The predominance of females over males is evident in both groups, being in a ratio of approximately two and a half to one for the adenomas and exactly two to one for the hyperplasias.

### *Number of Glands Enlarged*

TABLE III

*Data on Enlarged Glands*

| | |
|---|---|
| Available cases | 185 |
| Single gland enlarged | 146 |
| Multiple enlargements | 39 |
| (*a*) Two glands | 25 |
| (*b*) Three glands | 1 |
| (*c*) Four glands | 13 |

### *Site*

The data are distinctly inadequate. Of 119 single tumors in which location is recorded, 56 were on the right and 47 on the left. In 76 cases an attempt was made at more accurate localization and of these, 12 adenomas were found in one of the upper glands and 64 in one of the lower glands. This five to one ratio is of evident surgical value. Tumors of aberrant parathyroid glands are by no means infrequent — 6 have been found within the thyroid, 2 in the thymus,

and 9 have been described as retrosternal. Where two glands have been reported as enlarged any combination is possible, but again the lowers have been more frequently involved than the uppers.

### *Size*

The sizes of the tumors vary over an extreme range. Symptoms of hyperparathyroidism have been recorded with a tumor only twice the size of a normal gland. At the other end of the scale tumors have been recorded weighing as much as 300 gm. and Benjamins [18] described one as large as a "child's head."

### *Incidence of Osteitis Fibrosa and Renal Stones*

The presence of bone lesions is recorded in 116 of the 160 cases collected in Table VI, but in only 4 of the remainder were they specifically stated to be absent. A glance at the table where the cases have been listed in the order of their publication will show how rarely the relation was recognized by the earlier writers. Since an analogous situation still prevails in regard to renal stone formation, we have listed our cases separately in the following table. The value of routine blood calcium and phosphorus determinations in all cases of renal stone formation (Albright *et al.*[5]) is at once evident when the percentage of calculi in this series is compared with that in the previously reported cases. We have included only the cases in which a definite statement in regard to bone lesions was recorded.

TABLE IV

*Incidence of Osteitis Fibrosa and Renal Stones*

| | Present series | | Cases in literature | |
|---|---|---|---|---|
| | No. | % of total (25) | No. | % of total (119) |
| Osteitis fibrosa alone | 5 | 20 | 70 | 58.8 |
| Renal stones alone | 11 | 44 | 3 | 2.52 |
| Osteitis fibrosa plus stone | 9 | 36 | 46 | 38.6 |

When our own series of cases is divided into the hyperplastic and the adenomatous groups, 13 of the latter showed bone lesions, whereas the 5 clear cell hyperplasias fall into the group of renal stones without bone changes and only Case 23A, the chief cell hyperplasia, showed significant bone lesions. That this is the result of chance

sampling in too small a series of cases is at once apparent by reference to the group of 14 clear cell hyperplasias collected from the literature, all but 1 of which showed bone lesions. It is evident that either type of hyperparathyroidism may be associated with stone formation only, bone changes only, or the combination. As a rule stone formation comes first and bone lesions follow only after a period of years. When the average duration of symptoms in our cases showing only renal stones is calculated, it is 3.2 years, whereas the average duration in the cases with classical bone lesions is 8.6 years.

## Classification

As we have already briefly outlined in the introduction to our own series of case reports, we believe the fundamental line of division in the pathology of hyperparathyroidism lies between diffuse hyperplasia of all the parathyroid tissue and localized proliferation of only a portion, the remaining glandular tissue being histologically normal. In the first type diffuse enlargement of all the glands is to be expected; in the second type one or at most two will be involved. The division, however, judging from our own experience and the reports of others, cannot safely be made upon the number of grossly enlarged glands in each case. The degree of enlargement of individual glands varies greatly and though slight enlargement of every gland is probably always present in hyperplasia, the swelling of one or two glands may be so predominant that minor enlargement of the others might readily be overlooked, particularly under the exigencies of a surgical operation. In cases, however, where portions of all the parathyroids have been examined microscopically, as in Cases 17, 23, 25 and 23A of our series, and 32, 36 and 53 from the literature, the uniformity in histological appearance of all the glands, whether large or small, is at once apparent.

Fortunately, however, the histological picture of the hyperplastic gland, at least of the more common wasserhelle type, is so characteristic, so different from anything we have seen in the cases of single tumor formation that we believe a diagnosis of hyperplasia should be possible as a rule from the histological examination of a single gland, even from a frozen section during an operation. The uniform, giant sized clear cells, the acinar arrangement, the basal orientation of the nuclei form a readily recognizable picture (Figs. 8–11).

That hyperplasia of a different type, uniform proliferation of chief cells without significant vacuolization, can occur is shown by our Case 23A (Figs. 12 and 13) and by Cases 29 and 61 from the literature. Hyperplasia of this type, marked enough to cause significant tumor-like enlargement of the glands, is evidently rare since including our own case we have been able to find only three examples.

Another potential source of error in classification, if gross enlargement only is considered, lies in the confusion of multiple neoplasms with hyperplasias. Numbers 20 and 21 of our series are, we believe, cases in point. In Case 20 all four parathyroids were exposed at operation, two which were enlarged were resected and from the other two, which appeared normal, biopsies were taken. The biopsies show normal parathyroid tissue. The two enlarged glands are shown in Figs. 25 and 26. In contrast to the hyperplastic cases where every gland presents a uniform appearance, one of these tumors is frankly glandular in character, the other consists of solid masses of chief cells without evident arrangement. In Case 21 two tumors of identical appearance, the familiar chief cell adenoma, were found, but a rim of normal gland about one of the tumors definitely rules out diffuse hyperplasia. Bergstrand[21] twice demonstrated a rim of normal gland about each of a pair of localized tumors.

An attempt to classify the cases from the literature is admittedly dangerous but by limiting ourselves to cases in which a reasonably complete histological description is recorded or in which adequate illustrations allow us to judge for ourselves, we believe that a fairly accurate classification is possible. That several of the cases may have been misplaced is frankly admitted. One hundred and twenty-eight cases from the literature have been utilized. To these have been added, besides our own series of 25, an additional 9 unreported cases from other hospitals which the authors have been given the privilege of examining histologically.* In compiling the table single glandular enlargement has been automatically placed in the neoplastic group, cases with three or four enlarged glands in the hyperplastic one. Where two glands were enlarged we have attempted classification on the basis of the histological features. Five cases of multiple enlargement, 37, 62, 94, 141 and 159, we have felt unable to classify.

* These 9 cases, all single tumors, are distributed as follows: chief cell alone 3, chief cell with giant forms 1, transition wasserhelle 2, glandular and cystic 1, wasserhelle generalized 1.

The localized enlargements or neoplasms have been subdivided first into single and multiple groups and then classified on purely morphological grounds. The sequence of the classification (Table V)

TABLE V

*Classification of Cases*

| | Case Nos. in our series | No. in our series | No. in literature | Percent of total |
|---|---|---|---|---|
| *A.* Hyperplasia (multiple) (22 cases) | | | | 13.6 |
| 1. Wasserhelle, generalized | 15, 16, 17, 23, 25 | 5 | 14* | |
| 2. Chief | 23A | 1 | 2† | |
| *B.* Neoplasia (140 cases) | | | | 86.4 |
| 1. Single (128 cases) | | | | |
| (*a*) Chief cell types (114 cases) | | | | |
| (1) Chief cell alone | 6, 7, 9 | 3 | 59 | |
| (2) Chief cell with giant forms | 1, 11 | 2 | 3 | |
| (3) Transition wasserhelle | 3, 22, 8, 12, 14 | 5 | 17 | |
| (4) Transition oxyphil | 10, 19 | 2 | 6 | |
| (5) Glandular and cystic | 4, 13, 18 | 3 | 14 | |
| (*b*) Wasserhelle cell types (14 cases) | | | | |
| (1) Generalized | 2 | 1 | 11 | |
| (2) Focal | 5 | 1 | 1 | |
| 2. Multiple (12 cases) | | | | |
| (*a*) Chief cell types | 20, 21 | 2 | 7 | |
| (*b*) ? Oxyphil cell | | | 3 | |
| | | 25 | 137 | |

* Case Nos. 22, 23, 25, 32, 36, 53, 89, 92, 98, 123, 125, 126, 127, 155.
† Case Nos. 29, 61.

follows the order in which the case reports have been presented above.

Out of a total of 161 cases 22 or 13.6 per cent appear to belong in

the hyperplastic group, 19 of which are in the wasserhelle type as against 3 in the chief cell type. The far commoner localized tumor formation is represented by 140 cases, 86.4 per cent of the total, 130 of them single tumors, 10 of them multiple. In the single tumors the chief cell with its transition forms accounts for at least 90 per cent.

## Discussion

### *Hyperplasia versus Neoplasia*

Since the recognition of the syndrome of hyperparathyroidism, the question whether to regard the proliferative changes in the glands as hyperplastic or neoplastic has been a matter of controversy which the paucity of available evidence served only to stimulate. The demonstration of a distinct group of cases characterized by diffuse uniform involvement of all parathyroid tissue is, we believe, the first unequivocal evidence bearing on this issue. Such diffuse involvement points so strongly to hyperplasia dependent on a generalized humoral stimulus (possibly though improbably with mediation of the nervous system), and so strongly against a local autonomy that neoplasia cannot be seriously considered. The recognition, moreover, of at least two distinct histological types of hyperplasia not only suggests the interesting possibility of multiple potential stimulating factors but confirms the essential pattern of the hyperplastic lesion — the uniform diffuse involvement of all the glandular tissue. The analogy to exophthalmic goiter is of course apparent.

In sharp contrast to this relatively uncommon type of case stands the far more usual type of a localized proliferative process which leaves entirely uninvolved the remaining glandular tissue. Let us first consider several suggestive but inconclusive histological criteria favoring the neoplastic origin of the localized tumors (which our cases illustrate). All of them have been repeatedly cited before, but they rise in importance by their comparison with known hyperplastic lesions.

Cell size and number of nuclei fail to provide distinguishing criteria since rather surprisingly the hyperplastic group provides the largest cells and the most frequently multinucleated. But among the group of localized tumors an occasional example is encountered of gigantism of the nuclei up to 20 microns (Fig. 18) associated with an irregular multilobulated outline and extreme hyperchromatism,

which has no parallel in the hyperplastic state and which has a certain *prima facie* neoplastic quality.

In comparison with the rather monotonous uniformity as a group and also from field to field of the hyperplastic cases the localized tumors present a protean picture not merely as a group, but also at times within the dimensions of a low power field of a single tumor. Tumors may be made up almost solely of chief cells (Fig. 17), of fully developed wasserhelle cells (Fig. 16), of transitional wasserhelle (Fig. 19), of transitional oxyphil cells (Fig. 20), or any combination of these elements. Well developed gland formation will be present in one area, broad anastomosing cords in another and solid patternless cell masses in a third.

Fibrous stroma which is scant but uniform in its distribution in the normal gland increases in the hyperplastic gland to strands of uniform width which surround each acinus and sharply demarcate it from its neighbors. In the localized tumors, in contrast, it is markedly irregular in character and distribution, here abundant and richly collagenous, there tenuous and barely demonstrable. Blood vessels which are constant in size in the normal gland, rather uniformly increased in number and diameter in the hyperplastic gland, become irregular in caliber and distribution in the tumor nodules. A sinusoidal dilatation of capillary vessels is a frequent abnormality. Endothelial-lined spaces, probably lymphatics, which are undemonstrable in normal and hyperplastic glands, are frequently conspicuously dilated.

The crux of the argument rests, in our opinion, in the localized character of the proliferative process. Our own experience indicates this is frequently limited not merely to one gland but to a portion of a single gland. In 8 of our 19 adenomatous cases we have been able to demonstrate a rim of normal parathyroid tissue on one margin of the tumor. That this has been noted in the literature on only eight occasions can be explained we feel on two bases: (1) it has not been systematically looked for, and (2) our cases for the most part are early ones with relatively smaller tumors than the majority that have been reported. It is obvious that the mathematical chances of demonstrating a small fragment of normal parathyroid tissue in or on the capsule of a tumor diminish rapidly with increase in size of the tumor. Partial or total atrophy of the normal remnants is, moreover, not improbable with tumors of large size.

If an external humoral stimulus to overgrowth is present in these cases, it must be of minimal importance compared with the local autonomous factor which determines the site of the proliferative activity. Moreover, if the newgrowth were in response to a persisting outside stimulus, surgical removal should logically be followed by reasonably prompt recurrence of the growth process in one of the other remaining glands. Surgical experience does not support this in a wide experience with the localized tumors. In the realm of typical hyperplasias experience is still limited, but the short follow-up on our Cases 15 and 23 strongly suggests an extrinsic factor. In Case 23, three enlarged glands and a biopsy of a normal sized fourth gland were removed, following which the serum calcium fell from 13.1 to 10.18 mg. Three months later the serum calcium was 11.96 mg. Case 15, in which three enlarged glands were removed, with a drop of serum calcium to 11.4 mg., is awaiting further treatment with a serum calcium that has risen once more to 13.8 mg.*

We can, therefore, distinguish on the available evidence between two groups of proliferative changes in the parathyroid glands, one primarily dependent on an external, continuous stimulus, the second independent, as far as can be made out, of such a stimulus, determined in its localization and duration by local autonomous factors which can be extirpated by local surgical removal. This second type of proliferation, an essentially autonomous newgrowth, falls within the accepted limits of the term neoplasia.

### *Comparison of the Size of Hyperplastic Glands and Adenomas with the Degree of Hyperparathyroidism*

The degree of hypertrophy of glandular tissue in cases of parathyroid hyperplasia is in itself worthy of attention. The material removed from Case 16 of our series, the severest of our hyperplastic cases, amounted to 15.6 gm. This is approximately one hundred times the weight of the total normal parathyroid tissue. A degree of hyperplasia equal to this is totally unparalleled in human pathology. In exophthalmic goiter, in mazoplasia or in prostatic hyperplasia five or tenfold hypertrophy would be unusual. Even lactation hypertrophy of the breast is left far behind.

* A fourth gland in this case was not found and all of the third gland, except for a piece twice the size of a normal gland, was resected.

In the case of parathyroid adenomas still greater variations occur. In our Case 1 the tumor weighed 53 gm., approximately four hundred times the normal, and much larger tumors are on record. If this new-formed glandular tissue functioned in proportion to its size, some individuals would die of parathyroid poisoning, like that so easily produced in animals with parathormone,[77] unless some compensating mechanism were brought into play. An answer to the problem must await biological assays of material from both hyperplastic and adenomatous glands.

That a roughly quantitative relation between size of tumor and degree of hyperfunction exists is apparent from the following figures. Since weights were lacking on several of the cases, we have compared the volumes.

(5 cases) Blood calcium less than 12 mg. Average volume 255 cmm.
(9 cases) Blood calcium 12 to 14 mg. Average volume 3830 cmm.
(8 cases) Blood calcium greater than 14 mg. Average volume 16,000 cmm.

It is evident that as the size of the tumor increases the proportional effect of unit weight on the blood calcium becomes rapidly less and less. In fact in the hyperplastic cases the relation appeared to approach a logarithmic function. The hyperplasias, as might be expected from their histological uniformity, show a more nearly mathematical relation. The adenomas in contrast show far wider variations. All attempts to correlate the degree of hyperfunction with the histology of the tumors have proved fruitless.

### *Function*

Throughout the history of endocrinology the study of tumors of the ductless glands has played an important rôle, sometimes pointing the path to chemical researches, as in the case of the pituitary adenomas, sometimes bringing up the rear to give final confirmation to an already well understood mechanism, as in the pancreatic islet adenomas. The multiplicity of cell types in the parathyroid glands naturally makes one think of the pituitary. Does the study of parathyroid tumors aid us in understanding the histophysiology of the normal organ?

In the normal gland there is general agreement, and our own studies are in accord, that glycogen can invariably be found at any age and is present in every type of cell except the fully developed

oxyphil. Unfortunately, material was not suitably preserved for glycogen stains in all of our cases, but we have available at least 1 case of each type and as yet have not failed to demonstrate at least some granules. As a general rule it is less abundant in both the tumors and the hyperplasias than in the normal gland (in adenomas with normal tissue in the capsule this is often strikingly apparent) but in at least some cells of every tumor it will be found. It is apt to be most evident in the cells that approach most nearly the normal chief cell in appearance. It is present in the wasserhelle cells and it is least marked or absent in the cells that most nearly approach the normal oxyphils. We can, therefore, say that glycogen has been found present whenever sought for in every case of hyperfunction. This reinforces the fact that it is invariably present in the normal gland and suggests that glycogen is in some way necessary to the elaboration of the specific hormone.

Fat droplets within the parenchymal cells are in contrast entirely lacking in the normal glands of children and cannot, therefore, be necessary to the elaboration of the hormone by which the calcium balance is maintained. In confirmation, intracellular fat has been present in some of our adenomas, absent in others.

Fat cells in the stroma cannot seriously be considered to have any direct bearing on the function of the gland. They remind one naturally of the bone marrow, and their relative independence of the state of nourishment of the individual might suggest a similar function, a readily resorbable tissue permitting rapid and facile hyperplasia. In hyperplastic glands it entirely disappears; in the adenomas it is usually absent though occasional fat cells can be found.

Have the oxyphil cells a function? Certainly their presence is not necessary to the normal functioning of the gland since they appear only with middle age and do not become numerous until advanced life. Oxyphil cells are wholly absent from the hyperplastic physiologically overactive gland. True oxyphils may be wholly absent from the adenomas; they may be scattered in small numbers much as they are distributed in the normal gland of early adult life; they may be present in localized collections similar to the oxyphil islands of old age. Transition oxyphils, according to our classification cells with large amounts of homogeneous red cytoplasm but still with traces of vacuolization about the nucleus, may make up the bulk of a tumor, but among them cells which closely approach the chief cell type have

always been found. We have been unable to classify any of our cases as a true oxyphil adenoma and although cases have been so classified by other authors, we have not found their descriptions convincing. Turnbull's case of oxyphil adenoma (Case 93), for instance, clearly shows from an illustration some degree of halo formation about the nucleus. He himself speaks of the presence of glycogen and fat, though he has never been able to demonstrate these substances in the typical oxyphil cells of normal glands. We feel, therefore, that it can fairly be said that histological evidence fails to support the concept of the elaboration of parathyroid hormone by the oxyphil cells. The frequency of these cells in tumors, even in young people, their absence in hyperplasias, their increase under normal conditions in old age, all point toward an involution phenomenon. The possibility of another function, unconnected with the calcium metabolism cannot be ruled out, but we have found no evidence for it.

### *Interrelation Between Cells*

Since Welsh's fundamental study of the histology of the parathyroid glands, the interrelation of the various cell types has been under discussion. He sharply separated the oxyphil cell but believed in transitions between the water-clear and the chief cell, though he considered the former the more primitive type, in contrast to later workers, such as Getzowa,[56] who have felt that if one were derived from the other, it was the chief cell which was the primitive form.

With Kurokawa [85] the possibility that the oxyphil also was derived from the chief cell was considered and various transition forms were described. Hunter and Turnbull [80] have developed this concept, stating that "the oxyphil cells are principal cells in which the cytoplasm has been so charged with oxyphil granules that the basophil net has been more or less completely reduced to a limiting membrane."

Does a study of the tumors of the parathyroid glands contribute any evidence for or against a monophyletic development of the various cell types? As Hunter and Turnbull have pointed out, the normal evolution of the gland in fetal and adolescent life, starting only with chief cells, with successive development of water-clear cells, of pale oxyphils and dark oxyphils with the simultaneous appearance of transition forms argues for a single fundamental cell type. The clear

TABLE VI

*Summary of Case Reports from the Literature*

| Author | Year | Age in yrs. | Sex | No. of tumors | Site | Size in cm. | Weight in gm. | Bone change | Renal stone | Cell type | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. de Santi ..... | 1900 | 58 | M | 1 | | Very large | | | | No histology | |
| 2. Benjamins ..... | 1902 | 57 | M | 1 | R | Child's head | | | | Chief | |
| 3. Askanazy ..... | 1903 | 51 | F | 1 | L | 4.5 × 2 | | + | + | Chief | |
| 4. Erdheim ..... | 1903 | 18 | | 1 | RL | 2.5 × 1.5 × 1.5 | | | | Chief | |
| 5. MacCallum ..... | 1905 | 26 | M | 1 | RL | 2 × 2 × 2 | | | | Chief (occasional wasserhelle) | |
| 6. Hulst ..... | 1905 | old | F | 1 | In thyroid | 2.5 × 2.5 × 2 | | | | Transition wasserhelle | |
| 7. Weichselbaum ... | 1906 | | M | 1 | RL | 2.5 × 1.5 × 1.5 | | | | | Died of pneumonia |
| 8. Weichselbaum ... | 1906 | | F | 1 | LU | 4.3 × 3.6 × 1 | | | | ? Glandular and cystic | Died of pneumonia |
| 9. Langhans ..... | 1907 | 58 | M | 1 | | 13 × 9 × 8 | | | | Wasserhelle generalized | Operation for goiter |
| 10. Langhans ..... | 1907 | 60 | F | 1 | | 10 × 8 × 2 | | | | Wasserhelle generalized | Operation for goiter |
| 11. von Verebélÿ .... | 1907 | 42 | F | 1 | RL | 2.5 × 1.8 × 1.5 | | | | Chief (occasional wasserhelle) | |
| 12. von Verebélÿ .... | 1907 | 56 | M | 1 | LL | 1.2 × 0.8 × 0.3 | | | | Wasserhelle generalized | |
| 13. Schmorl ..... | 1907 | 48 | F | 1 | LU | 2.8 × 1.8 × 0.5 | | + | | Chief | |
| 14. Thompson and Harris ..... | 1908 | 23 | F | 1 | | 15 × 10 × 6 | 250 | | | Chief | Operation for goiter |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15. Bérard and Alamartine ... | 1908 | 43 | F | 1 | L | 2 × 1.5 | | | | Chief (occasional wasserhelle) | |
| 16. Pepere ..... | 1907 | 40 | F | 1 | LU | Apple sized | | | | Chief | |
| 17. DaCosta ..... | 1909 | 32 | F | 1 | R | Orange sized | | | | Glandular and cystic | Operation for goiter |
| 18. Strada ..... | 1909 | 54 | F | 1 | R | 2.8 × 1.4 × 0.9 | | + | + | Chief (occasional wasserhelle) | 4 other glands slightly enlarged. ? osteomalacia |
| 19. Claude and Schmiergeld ... | 1909 | 85 | M | 1 | RL | 1.5 × 0.7 × 0.5 | | | | Wasserhelle generalized | Epilepsy |
| 20. da Costa ..... | 1909 | 50 | F | 1 | RL | | | | | Glandular and cystic | |
| 21. Gussio ..... | 1910 | 30 | F | 1 | L | Small mandarin | | | | Chief | |
| 22. Möller ..... | 1911 | 72 | F | 2 | LU<br>RU | 2 × 1.2 × 1<br>0.8 × 0.6 × 0.4 | | | | Wasserhelle generalized | Lowers not found |
| 23. Möller ..... | 1911 | 46 | F | 2 | LU<br>RU | 4.5 × 0.5 × 0.5<br>4.5 × 0.5 × 0.5 | | | | Wasserhelle generalized | Miliary tuberculosis |
| 24. Ikonnikoff ..... | 1912 | 57 | F | 1 | In thyroid | Mandarin | | | | Chief | |
| 25. Gjestland ..... | 1912 | 75 | M | 2 | RL<br>LL | 4 × 1<br>Hazel nut | | o | o | Wasserhelle generalized | Uppers slightly enlarged |
| 26. Schmorl ..... | 1913 | 72 | M | 1 | U | | | ? Paget's | | No histology | |
| 27. Molineus ..... | 1913 | 74 | F | 1 | R | 2.7 × 1.7 × 0.7 | | + | | Transition wasserhelle | |

R = right; L = left or lower; U = upper.

TABLE VI (*continued*)

| Author | Year | Age in yrs. | Sex | No. of tumors | Site | Size in cm. | Weight in gm. | Bone change | Renal stone | Cell type | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 28. Molineus ..... | 1913 | 59 | F | 2 | LU<br>RL | 2.7 × 1.8 × 0.8<br>2.7 × 1.8 × 0.8 | | + | | Chief (? transition wasserhelle) | 2 others normal |
| 29. Molineus ..... | 1913 | 48 | F | 4 | RU<br>RL<br>LU<br>LL | 1.8 × 1.2 × 0.2<br>1.9 × 1.7 × 0.8<br>1.6 × 0.4 × 0.3<br>2.3 × 1.1 × 1.2 | | + | | Chief (papillary) | |
| 30. Paltauf ..... | 1913 | 51 | F | 1 | RL | | | + | | Chief | 3 others normal |
| 31. Harbitz ..... | 1915 | 26 | F | 1 | L | 3.5 × 3.5 × 2 | | + | + | Chief | Called osteomalacia |
| 32. Harbitz ..... | 1915 | 75 | M | 4 | RU<br>RL<br>LU<br>LL | 4 × 1<br>Pea<br>2 × 2.5<br>1 × 1.2 | | | | Wasserhelle generalized | Paralysis agitans |
| 33. Harbitz ..... | 1915 | 32 | F | 1 | LL | 11 × 5 | | | | ? transition oxyphil | Died of tuberculosis |
| 34. Maresch ..... | 1916 | 69 | M | 1 | L | 7 × 4 × 1.5 | | o | | Glandular and cystic | 3 others normal |
| 35. Meyer ..... | 1917 | 36 | M | 1 | RL | 4 × 3 | | + | | Chief | 3 others normal |
| 36. Bergstrand ..... | 1920 | 57 | F | 4 | | | 0.40<br>0.15<br>0.08<br>1.04 | o | o | Wasserhelle generalized | Died of pneumonia |
| 37. Hubbard and Wentworth ... | 1921 | 20 | F | 2 | | 2 in diameter | | + | + | Called hyperplasia | ? renal rickets |
| 38. Hartwich ..... | 1922 | 60 | F | 1 | L | 7 × 2.5 × 1 | 4.9 | + | | Chief (occasional wasserhelle) | Others normal |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 39. Nägelsbach and Westnes ..... | 1922 | 27 | M | 1 | | Pigeon's egg | | + | + | No histology | Others normal |
| 40. Günther ..... | 1922 | | | 1 | RL | | | + | | Chief | History lost |
| 41. Fischer ..... | 1922 | 46 | M | 1 | RL | 3.7 × 2.7 × 2 | | + | | No histology | |
| 42. Strauch ..... | 1922 | 27 | F | 1 | L | 4.8 × 3.2 × 3.5 | | | | ? oxyphil (wasserhelle) | Puerperal osteomalacia |
| 43. Sauer ..... | 1922 | 21 | M | 1 | LL | Hazel nut | | + | + | Chief | Calcified capsule |
| 44. Bergstrand ..... | 1922 | 21 | F | 2 | RL<br>LL | | 0.31<br>0.32 | | | ? transition oxyphil | Uppers normal. Thymus enlarged |
| 45. Bergstrand ..... | 1922 | 58 | F | 2 | RL<br>LL | | 0.12<br>0.37 | | | ? transition oxyphil | Uppers normal. Thymus enlarged |
| 46. Pachner | 1922 | 52 | F | 1 | L | 15 × 10 | | | | ? transition wasserhelle | |
| 47. Dawson and Struthers ..... | 1923 | 49 | M | 1 | LL | 2.5 in diameter | | + | | Chief | |
| 48. Fasiani ..... | 1923 | 65 | F | 1 | | Fist | | | | Chief (occasional wasserhelle) | |
| 49. Stenholm ..... | 1924 | 24 | M | 1 | RL | 1.8 × 1.2 × 1 | | + | + | Chief | 3 others normal |
| 50. Stenholm ..... | 1924 | 52 | F | 1 | RL | 3.3 × 1.9 × 1.1 | | + | | Glandular and cystic | 3 others normal |
| 51. Chauveau ..... | 1925 | 50 | F | 1 | | Hazel nut | | + | | Chief | |
| 52. Gödel, Leb ..... | 1925 | 42 | F | 2 | LL<br>RL | 10 × 2<br>8 × 1.8 | | + | + | Chief (? transition wasserhelle) | |
| 53. Hoffheinz ..... | 1925 | 42 | | 4 | RL<br>RU<br>LL<br>LU | 5.5 × 3.4 × 1.4<br>2 × 0.5 × 0.3<br>4.5 × 2.1 × 1.2<br>1.4 × 1 × 0.3 | | | | Wasserhelle generalized | |

TABLE VI (*continued*)

| Author | Year | Age in yrs. | Sex | No. of tumors | Site | Size in cm. | Weight in gm. | Bone change | Renal stone | Cell type | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 54. Penecke ..... | 1926 | 38 | F | 1 | LL | | 16 | + | + | ? transition oxyphil | Chronic nephritis |
| 55. Penecke ..... | 1926 | 59 | F | 1 | RL | | 5 | | | Chief | Erysipelas |
| 56. Mandl ..... | 1925<br>1926 | 38 | M | 1 | LL | 2.5 × 1.5 × 1.2 | | + | | Transition wasserhelle | |
| 57. Parreira and Castro Freire | 1926 | 16 | M | 1 | R | Chestnut | | + | | Wasserhelle generalized | |
| 58. Hendriock ..... | 1926 | 71 | F | 1 | Retro-sternal | 8 × 5 × 4.5 | | | | Wasserhelle | |
| 59. Wanke ..... | 1926 | 31 | F | 1 | RL | Chestnut | | + | + | Chief | |
| 60. Gold ..... | 1928 | 54 | F | 1 | RU | 2.5 × 1.6 | | + | | Chief (? transition wasserhelle) | |
| 61. Bergstrand ..... | 1928 | 48 | F | 4 | | | Total 13.7 | | | Glandular and cystic | Cerebral hemorrhage |
| 62. Beck ..... | 1928 | 41 | F | 2 | RL<br>LL | Coffee bean<br>Hazel nut | | + | | No histology | |
| 63. Eggers ..... | 1929 | | F | 1 | LL | Hazel nut | | + | | No histology | |
| 64. Boyd *et al.* ..... | 1929 | 21 | M | 1 | LL | 3.5 × 2.5 | | + | | Transition wasserhelle | |
| 65. Barr *et al.* ..... | 1929 | 56 | F | 1 | L | 3 in diameter | | + | + | Chief | |
| 66. Barr *et al.* ..... | 1929 | 38 | M | 1 | | 5 in diameter | | + | | Chief | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 67. Guy ..... | 1929 | 29 | F | 1 | | 8 × 6 × 4 | | | | Glandular and cystic | Recurred |
| 68. Hunter ..... | 1929 | 41 | F | 1 | LL | 3.7 × 3 × 3 | | + | | No histology | |
| 69. Wellbrock ..... | 1929 | 32 | F | 1 | Retro-sternal | 5 × 3.5 × 3 | | + | | Glandular and cystic | |
| 70. Lloyd ..... | 1929 | 22 | F | 2 | LL<br>RL | 1.7 × 1 × 0.8<br>1.5 × 0.4 × 0.3 | | | | Chief (occasional wasserhelle) | Pituitary tumor |
| 71. Drennan ..... | 1930 | 63 | F | 1 | RL | 4.5 in diameter | | + | | Chief (occasional wasserhelle) | |
| 72. Zajewloschin .... | 1930 | 57 | M | 1 | RL | 4.3 × 3 × 1.3 | 8 | | | Chief | Others normal |
| 73. Pemberton ..... | 1930 | 14 | F | 1 | LL | 1.5 × 1.3 × 1.3 | | + | | Chief | |
| 74. Compere ..... | 1930 | 59 | F | 1 | LL | 1 × 1.8 | | + | | Glandular and cystic | |
| 75. Snapper ..... | 1930 | 56 | M | 1 | LL | 2.5 × 1.4 | | + | | Wasserhelle generalized | |
| 76. Rosenbach and Disqué ..... | 1930 | 24 | F | 1 | RL | | | + | | No histology | |
| 77. Hecker ..... | 1930 | | | | | Walnut | | + | | No histology | |
| 78. Ask-Upmark .... | 1930 | 46 | M | 1 | L | 1.5 × 1.2 × 1.2 | | + | o | Chief | |
| 79. Léri *et al.* ..... | 1930 | 31 | M | 1 | RL | | | + | + | Wasserhelle generalized | |
| 80. Wanke ..... | 1930 | 38 | F | 1 | RL | Walnut | | + | + | Glandular | |
| 81. Wanke ..... | 1930 | 41 | F | 2 | RU<br>RL | Coffee bean<br>Almond | | + | + | Chief | |
| 82. Schupp ..... | 1931 | 51 | F | 1 | In thyroid | 1.5 × 0.5 × 0.8 | | + | | Chief | 3 others normal |

TABLE VI (*continued*)

| Author | Year | Age in yrs. | Sex | No. of tumors | Site | Size in cm. | Weight in gm. | Bone change | Renal stone | Cell type | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 83. Schouten ..... | 1931 | 55 | M | 1 | | | | + | | No histology | |
| 84. Silvestrini ..... | 1931 | 25 | M | 1 | L | Olive | | + | | No histology | |
| 85. Silvestrini ..... | 1931 | 57 | M | 1 | L | 1.5 × 2.5 | | + | | No histology | |
| 86. Allan ..... | 1931 | 34 | M | 1 | | | 10 | + | | No histology | |
| 87. Snapper ..... | 1931 | 35 | F | 1 | L | Almond | | + | | No histology | |
| 88. Quick and Hunsberger, Schnabel | 1931 | 25 | M | 1 | Retro-sternal | 5.2 × 3.5 × 2.5 | | + | + | Chief | Removed in two operations |
| 89. Paul ..... | 1931 | 56 | M | 2 | RU<br>LU | 6 × 3 × 3<br>6 × 3 × 3 | | + | + | Wasserhelle generalized | Adrenals enlarged |
| 90. Cosin ..... | 1931 | 17 | M | 1 | RU | 2.7 × 2.2 × 2 | | + | + | Transition wasserhelle | |
| 91. Hunter and Turnbull ..... | 1931 | 49 | F | 2 | LU<br>RL | 1.1 in diameter<br>2.8 × 1.8 × 2.5 | | + | + | Chief with giant forms | |
| 92. Hunter and Turnbull ..... | 1931 | 37 | F | 2 | RU<br>LL | 2.3 × 1.5 × 0.9<br>1.4 × 0.8 × 0.5 | | + | + | Wasserhelle generalized | |
| 93. Hunter and Turnbull ..... | 1931 | 49 | F | 1 | LL | 6.8 × 2.8 × 1.4 | 13.5 | + | + | ? oxyphil ? wasserhelle | |
| 94. Hunter and Turnbull ..... | 1931 | 51 | F | 2 | RU<br>RL | 7.5 × 5 × 1.8<br>2 × 1.3 × 1.2 | 26.2 | + | + | Called oxyphil | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 95. Lièvre *et al.* ..... | 1931 | 41 | F | 1 | RL | 3.5 × 3 × 2 | | + | | ? transition oxyphil | |
| 96. Cooley ..... | 1931 | 14 | F | 1 | | | | + | | No histology | |
| 97. Ask-Upmark .... | 1931 | 43 | F | 1 | L | 4 × 2.2 × 1 | | + | | Chief | |
| 98. Bergstrand ..... | 1931 | 55 | F | 2 | LU<br>RL | 4.5 × 2.5 × 3<br>4.5 × 2 × 0.5 | | + | + | Wasserhelle generalized | 2 others slightly enlarged |
| 99. Berner ..... | 1931 | 40 | F | 1 | L | 1.8 × 1.8 | 7 | + | | Wasserhelle focal | |
| 100. Berner ..... | 1931 | 47 | F | 1 | L | 3 in diameter | | + | + | Chief (occasional wasserhelle) | |
| 101. Fraser ..... | 1931 | 42 | F | 1 | | | | + | | No histology | |
| 102. Fraser ..... | 1931 | 26 | F | 1 | | | | + | + | No histology | |
| 103. Fraser ..... | 1931 | 23 | F | 1 | | | | + | + | No histology | |
| 104. Weil ..... | 1931 | 44 | F | 1 | RL | 3.1 × 2.2 × 1.6 | 4.3 | + | + | No histology | |
| 105. von Redwitz .... | 1931 | | | 1 | RL | Cherry stone | | + | | No histology | |
| 106. May and Lièvre | 1931 | 45 | M | 1 | LL | 3 × 2 × 0.8 | 1.8 | + | + | Chief | |
| 107. Chievitz and Olsen ..... | 1932 | 25 | F | 1 | RL | 3.5 × 2 × 0.5 | | + | | Chief | |
| 108. Noble ..... | 1932 | 40 | M | 1 | LU | 2 × 1.8 × 1.5 | | + | + | Transition wasserhelle | |
| 109. Hadfield and Rogers ..... | 1932 | 58 | F | 1 | L | 5 × 3.5 × 3 | 52 | 0 | | ? wasserhelle generalized | Acromegaly |
| 110. Hadfield and Rogers ..... | 1932 | 51 | M | 1 | | 8 × 4 × 2.5 | | | + | Chief | Acromegaly |

TABLE VI (*continued*)

| Author | Year | Age in yrs. | Sex | No. of tumors | Site | Size in cm. | Weight in gm. | Bone change | Renal stone | Cell type | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 111. Gaudier and Patoir ..... | 1932 | 60 | M | 1 | RL | | | + | | Glandular | |
| 112. Beyerinck ..... | 1932 | 35 | F | 2 | R and L | | | | + | Called tubular adenoma | 1 at operation<br>1 at autopsy |
| 113. Frugoni and Alessandri .... | 1932 | 18 | F | 1 | R | 2.2 × 1.1 × 0.6 | 0.9 | + | | Transition wasserhelle | |
| 114. Rosedale ..... | 1932 | 50 | F | 1 | R | 2 × 2.5 | 7 | + | | Transition wasserhelle | |
| 115. Mertz ..... | 1932 | 70 | F | 1 | RL | 1 × 1 × 0.5 | | + | | Glandular and cystic | |
| 116. Mertz ..... | 1932 | 64 | F | 1 | RL | Normal | | + | | Chief | Calcium high<br>Phosphorus low |
| 117. Mertz ..... | 1932 | 73 | F | 1 | RL | 1 × 0.5 × 0.5 | | + | | Chief | |
| 118. Morelle ..... | 1932 | 56 | F | 1 | LL | 6 × 6.8 × 4.2 | 67 | + | + | Chief | |
| 119. Coryn ..... | 1932 | 20 | F | 1 | In thyroid | 1.3 in diameter | | + | | Chief | 3 operations to find tumor |
| 120. Babcock ..... | 1932 | 25 | F | 1 | LL | 1.5 in diameter | | + | + | No histology | |
| 121. Wichmann ..... | 1932 | 45 | F | 1 | LU | 1.3 in diameter | | + | | Wasserhelle generalized | |
| 122. Hellström ..... | 1932 | 42 | F | 1 | LL | 2 × 1.8 × 1.4 | | + | | Chief | |
| 123. Hellström ..... | 1932 | 44 | F | 2 | R<br>L | Walnut<br>Walnut | | + | | Wasserhelle generalized | Removed at 3 months interval |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 124. Hanke ..... | 1932 | 33 | F | 2 | R<br>L | 3.1 × 3 × 1.2<br>Hazel nut | | + | + | Called oxyphil | |
| 125. Hanke ..... | 1932 | 49 | F | 2 | RL<br>LL | 5 × 3 × 2<br>Walnut | | + | + | Wasserhelle generalized | 2 others slightly enlarged |
| 126. Gordon-Taylor .. | 1932 | 20 | F | 2 | R<br>L | 3.5 × 2.5 × 2.5<br>Enlarged | | + | | Wasserhelle generalized | |
| 127. Wilder *et al.* ..... | 1932 | 48 | F | 1 | RU | 2 × 1.5 × 1 | | + | | Wasserhelle generalized | 3 others slightly enlarged. Same histology |
| 128. Rusakov and Sakayan ..... | 1932 | 50 | F | 2 | L<br>R | Cherry stone<br>3 × 2 × 1 | | + | + | Chief (occasional wasserhelle) | |
| 129. Renaud *et al.* ..... | 1932 | | | 1 | Retrosternal | 4 × 2.5 | | + | | Chief (occasional wasserhelle) | |
| 130. Cohen and Kelly ..... | 1933 | 48 | F | 1 | RL | 2.5 × 1.5 × 1 | 2.5 | + | + | Chief | |
| 131. Elmslie *et al.* .... | 1933 | 42 | F | 1 | LL | 3 × 1.5 × 1.5 | | + | o | Transition wasserhelle | |
| 132. Elmslie *et al.* .... | 1933 | 26 | F | 1 | R | 2.5 × 2 × 2 | | + | + | Transition wasserhelle | |
| 133. Elmslie *et al.* .... | 1933 | 23 | F | 1 | L | 3.5 × 1.5 × 0.7 | | + | + | Chief | |
| 134. Thomason and Smith ..... | 1933 | 41 | F | 1 | LU | 2.2 in diameter | | + | | Chief | |
| 135. Struthers ..... | 1933 | 38 | F | 1 | R | 1.8 in diameter | | + | | ? Chief | |
| 136. Struthers ..... | 1933 | 48 | F | 1 | | 1.8 in diameter | | + | + | No histology | |

TABLE VI (*continued*)

| Author | Year | Age in yrs. | Sex | No. of tumors | Site | Size in cm. | Weight in gm. | Bone change | Renal stone | Cell type | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 137. Copello and Barlaro ..... | 1933 | 46 | M | 1 | LL | | | + | + | Called adenoma | |
| 138. Venables ..... | 1933 | 52 | F | 1 | In thyroid | 1.8 × 1.8 × 1.2 | | + | | Called oxyphil | |
| 139. Rankin and Priestly ..... | 1933 | 34 | F | 1 | R | 6 in diameter | | + | | Chief with giant forms | |
| 140. Schlesinger and Gold ..... | 1933 | 42 | F | 1 | In thyroid | 5 × 4 × 4 | | + | | Glandular and cystic | |
| 141. Sainton *et al.* .... | 1933 | 43 | M | 2 | LL<br>LU | Enlarged | 2.1 | + | | ? oxyphil<br>? wasserhelle generalized | Calcium high after a 1st operation.<br>LU found at 2nd operation |
| 142. Keynes and Taylor ..... | 1933 | 18 | M | 1 | LL | 3.5 × 2.5 | | + | + | Chief | |
| 143. Dyke *et al.* ..... | 1933 | 14 | F | 1 | LL | 3 × 2 × 1 | | + | | Transition wasserhelle | |
| 144. Dyke *et al.* ..... | 1933 | 14 | F | 1 | RL | | 5 | + | | Transition wasserhelle | |
| 145. Abel *et al.* ..... | 1933 | 58 | F | 1 | LL | 4 × 1.8 × 1.6 | 4.3 | + | | Chief with ? giant forms | |
| 146. Mandl ..... | 1933 | 47 | F | 1 | Retrosternal | 4 × 2.5 × 2 | | + | | Chief | |
| 147. Hand ..... | 1933 | 39 | M | 1 | LL | 4 × 2.5 × 2 | | o | o | Glandular and cystic | Pyelonephritis |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 148. Morton ..... | 1933 | 20 | F | 1 | RL | 2.1 × 1.8 × 0.5 | 1.3 | + | | Transition wasserhelle | Other glands negative |
| 149. Schwensen and Eiken ..... | 1933 | 36 | F | 1 | | 5 × 3.5 × 2 | 37 | + | + | Chief | |
| 150. Khurgina ..... | 1933 | 34 | M | 1 | LL | 2.5 × 1 | | + | + | Chief | Diffuse calcium deposits |
| 151. Mimpriss and Butler ..... | 1934 | 17 | M | 1 | Retrosternal | 1.2 in diameter | | + | | Chief (occasional wasserhelle) | |
| 152. Barker ..... | 1934 | 65 | F | 1 | RL | 2.5 × 2 × 1 | | + | + | No histology | |
| 153. Strandgaard .... | 1934 | 47 | F | 1 | R | 1 × 1.7 | 2 | + | + | Transition wasserhelle | |
| 154. Sørensen ..... | 1934 | 74 | M | 1 | LL | 1.5 × 3.5 × 2.5 | 7 | + | | Chief | |
| 155. Capps ..... | 1934 | 50 | M | 2 | RL<br>LL | 7 × 3.5 × 2.1<br>2.4 × 3.5 × 2.1 | 22<br>13.6 | | | Wasserhelle generalized | |
| 156. Gutman *et al.* .... | 1934 | 34 | M | 1 | RL | 2.7 × 1.6 × 1 | 3.5 | + | ? + | Chief | |
| 157. Gutman *et al.* .... | 1934 | 53 | F | 1 | RL | 3 × 2 × 0.8 | 4.5 | + | + | Wasserhelle generalized | |
| 158. Gutman *et al.* .... | 1934 | 35 | F | 1 | | | | + | | No histology | |
| 159. Gutman *et al.* .... | 1934 | 60 | F | 2 | RU<br>RL | 2 in diameter<br>1.5 × 0.7 × 0.4 | | + | | Called oxyphil | |
| 160. Bergstrand ..... | 1934 | 64 | F | 1 | In thymus | Pigeon egg | | + | + | Chief | 4 others normal, adrenals enlarged, metastasizing thyroid adenoma |

cell hyperplasias prove that a physiological stimulus can convert every parathyroid cell into the wasserhelle type.

The neoplasias of the glands serve to reinforce the arguments against generically different cell types and favor the concept of a fundamental cell from which all others are derived. Pure tumors of either the oxyphil or wasserhelle type unaccompanied by any chief cell forms were not present in our series and we find the occasional reports in the literature unconvincing. When cells of either of these specialized types are predominant numerous transition forms of the chief cell can always be demonstrated. The chief cell in other words is the only invariable component of a tumor, obviously the basic fundamental cell and possibly the only proliferative form. The other cell types derived from it are to be regarded as degrees of differentiation or as involution forms.

## Summary

The histology of the parathyroid glands in 25 cases of hyperparathyroidism has been reported in detail and contrasted with the normal glands removed from 150 routine autopsies. It was found possible to divide the cases sharply into two groups, one of them characterized by diffuse uniform changes throughout all the glandular tissue—an obvious hyperplastic process—the second by a proliferative area limited to one gland, frequently even to a portion of it, or rarely involving parts of two glands. For reasons which have been discussed at length in the text, we regard this localized type of growth as neoplastic.

On this basis a classification of the parathyroid changes in hyperparathyroidism into two primary groups, hyperplasia and neoplasia, with subgroups under each heading, based on the morphological criteria of predominant cell type and structure, has been proposed. It has been shown that this is applicable not only to our own series but to the entire group of 160 cases which we have been able to collect from the literature.

An effort has been made to compile adequate statistical data on the relative frequency of these types of hyperparathyroidism and also on age and sex incidence, the frequency of multiple growths, the location of the tumors and the relation of both types of the disease to osteitis fibrosa cystica and to renal stone formation. A rough quan-

titative relation between the size of the enlarged glands and the degree of hyperfunction has been demonstrated.

Finally, an attempt has been made to bring to bear such data as a study of parathyroid tumors affords upon the problems of the function and the histogenesis of the various cell types.

## Conclusions

1. The pathological findings in the parathyroid glands in hyperparathyroidism may be divided sharply into two types, hyperplasia and neoplasia.

2. Hyperplasia is characterized by diffuse uniform involvement of all the glandular tissue. It occurs, however, in two forms, a wasserhelle or water-clear cell type, and a much rarer chief cell type.

3. Localized tumors of a single gland, part of a gland, or rarely parts of two glands, are more logically to be regarded as neoplasms.

4. A roughly quantitative relation between the size of the enlarged glands and the degree of hyperfunction exists.

5. The histology of parathyroid tumors provides confirmatory evidence for the monophyletic theory of origin of the various cell types.

6. Glycogen, albeit in minute amounts, is always present in functioning parathyroid tissue and the concept of the oxyphil cell as an inactive involution product receives support from a study of the adenomas.

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## DESCRIPTION OF PLATES

### PLATE 1

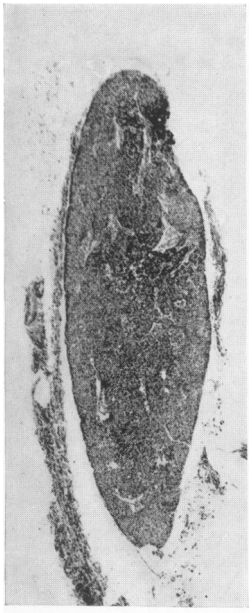
FIG. 1. A longitudinal section of a whole parathyroid gland from a child 16 months old, showing the compact grouping of the chief cells and the absence of fat. × 20.

FIG. 2. A longitudinal section of a whole normal parathyroid gland from an adult 40 years of age, showing the relative proportions of parenchymal and fat cells. × 15.

FIG. 3. A longitudinal section of a whole normal parathyroid gland from an adult 80 years of age, showing numerous circumscribed islands of pale oxyphil cells. × 15.

FIG. 4. A longitudinal section of a whole parathyroid gland showing a large cyst and two minute encapsulated adenomas. × 12.

FIG. 5. A longitudinal section of a whole parathyroid gland showing an apparently non-functioning, well circumscribed adenoma. Fat cells which are in normal numbers in the surrounding gland are nearly absent in the tumor. × 12.



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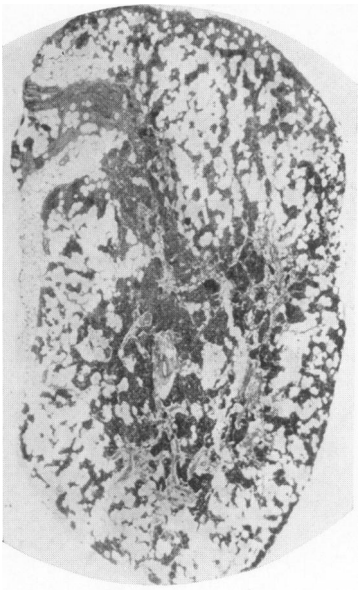

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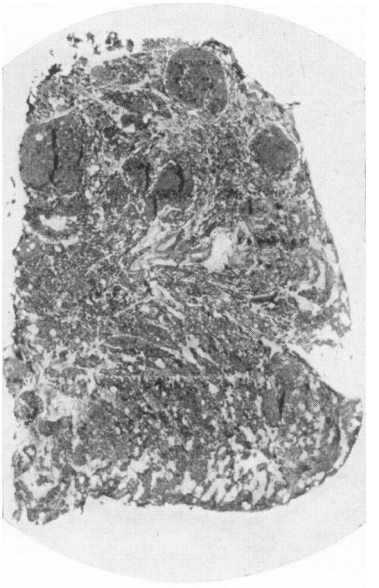

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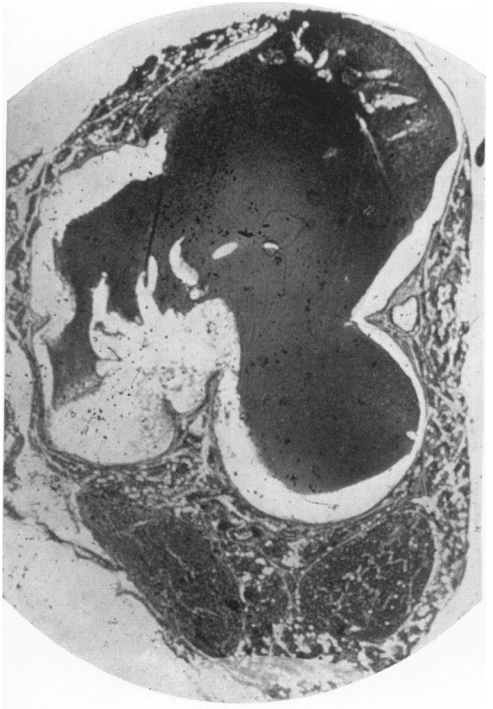

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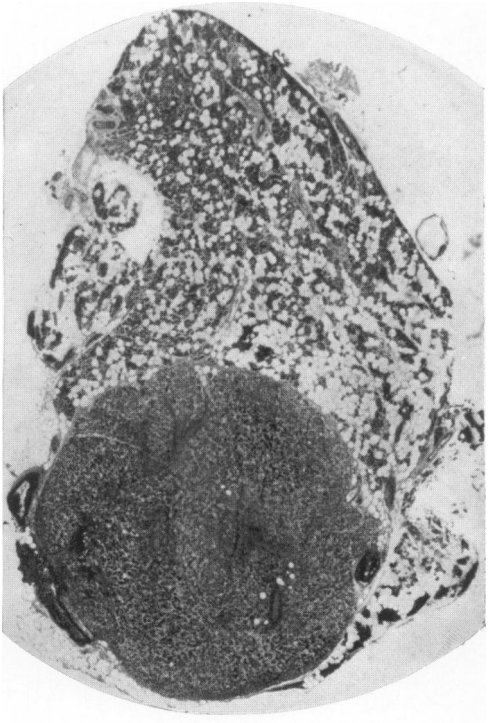

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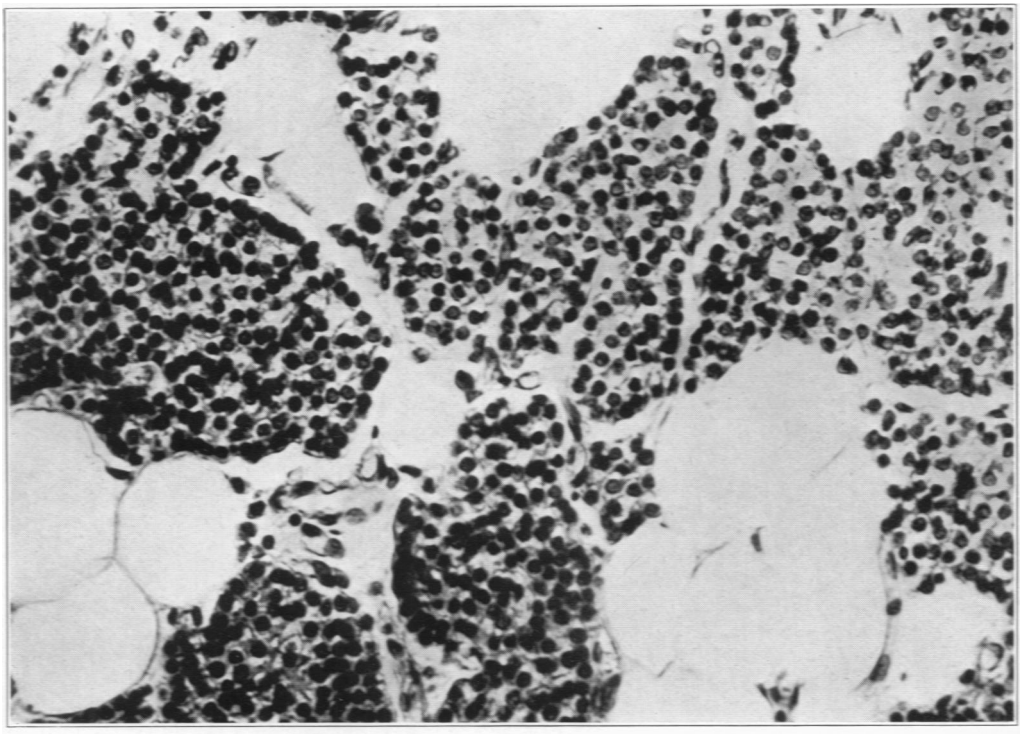
Castleman and Mallory

Pathology of Parathyroid Gland

## Plate 2

Fig. 6. A higher magnification of a small portion of the gland shown in Fig. 2, showing the normal chief and large fat cells. × 400.

Fig. 7. A higher magnification of an island of pale oxyphil cells from the gland shown in Fig. 3. Note the surrounding normal chief cells and the lack of extracellular fat globules. × 400.



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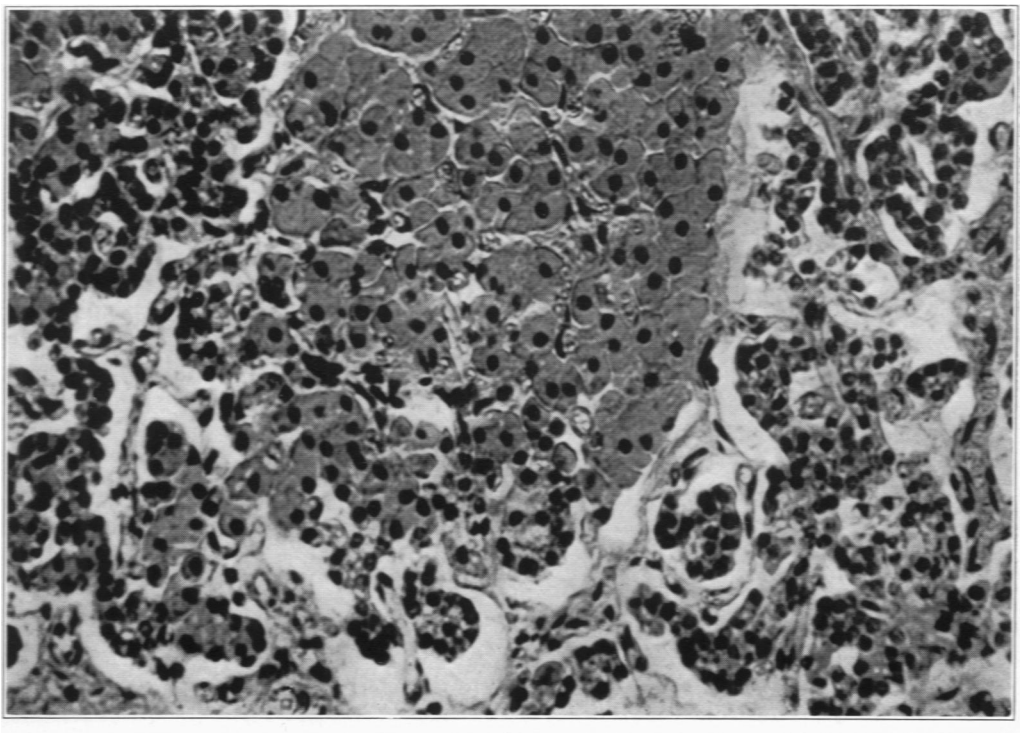

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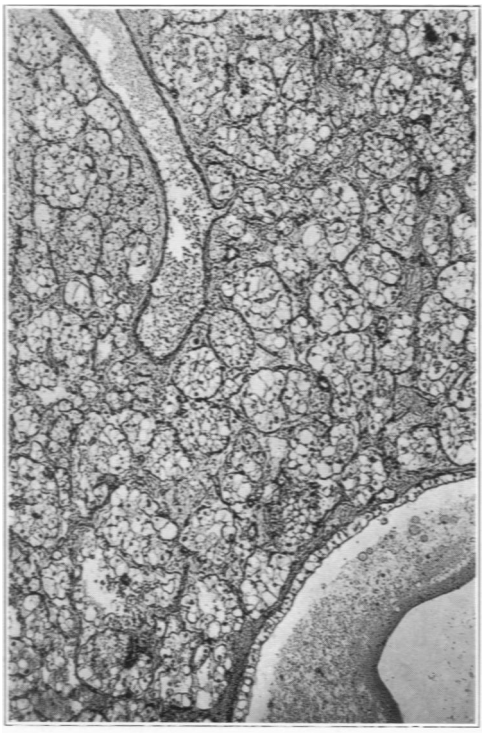
## PLATE 3

FIG. 8. Case 15. A low power view of clear cell hyperplasia. The marked uniform acinar arrangement, the swollen clear cells, the abundant vascular stroma and the absent fat are characteristic. One huge cyst is present. × 50.

FIG. 9. A higher power of Fig. 8. Note the definite gland formation, the sharply outlined large epithelial cells, the cytoplasm absent except for scattered granules, and the dark basally oriented nuclei. × 400.

FIG. 10. Case 16. The typical pattern in a case of parathyroid hyperplasia produced by the basal orientation of the nuclei. × 50.

FIG. 11. A higher power of Fig. 10. The nuclei of many of the cells lie out of the plane of section. When present, they are hyperchromatic and clearly oriented toward the stroma. × 400.



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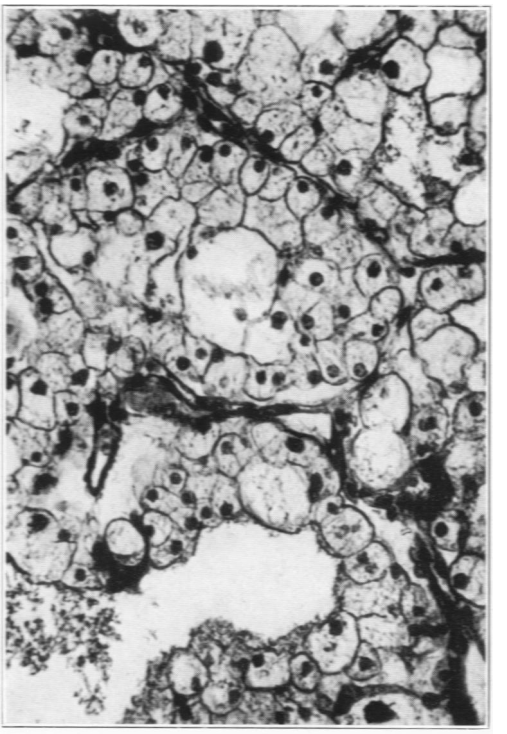

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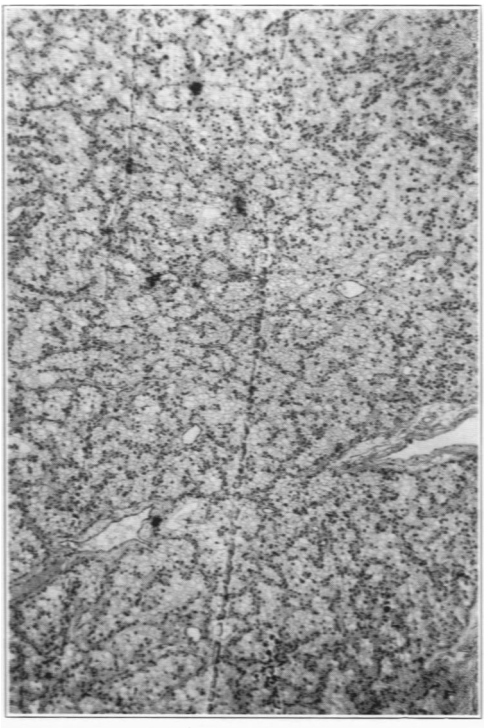

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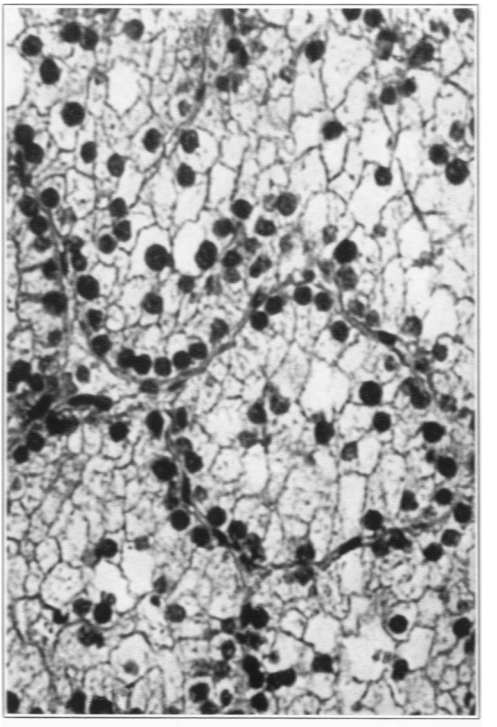

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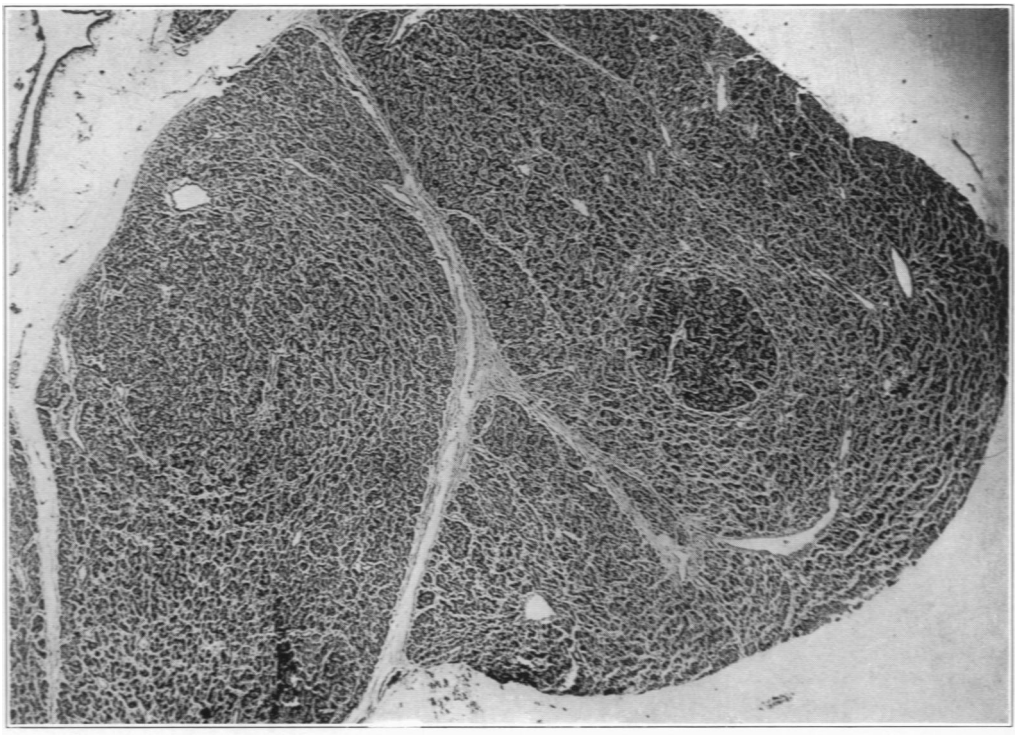
Castleman and Mallory

Pathology of Parathyroid Gland

## PLATE 4

FIG. 12. Case 23A. A case of parathyroid hyperplasia of the chief cell type. Note the compactness of the cell arrangement, the absence of intercellular fat and the papillary acinar arrangement in one area. × 30.

FIG. 13. A higher power of Fig. 12 taken at the edge of the large circumscribed papillary area, showing the marked basophilism in contrast to the surrounding tissue. × 400.



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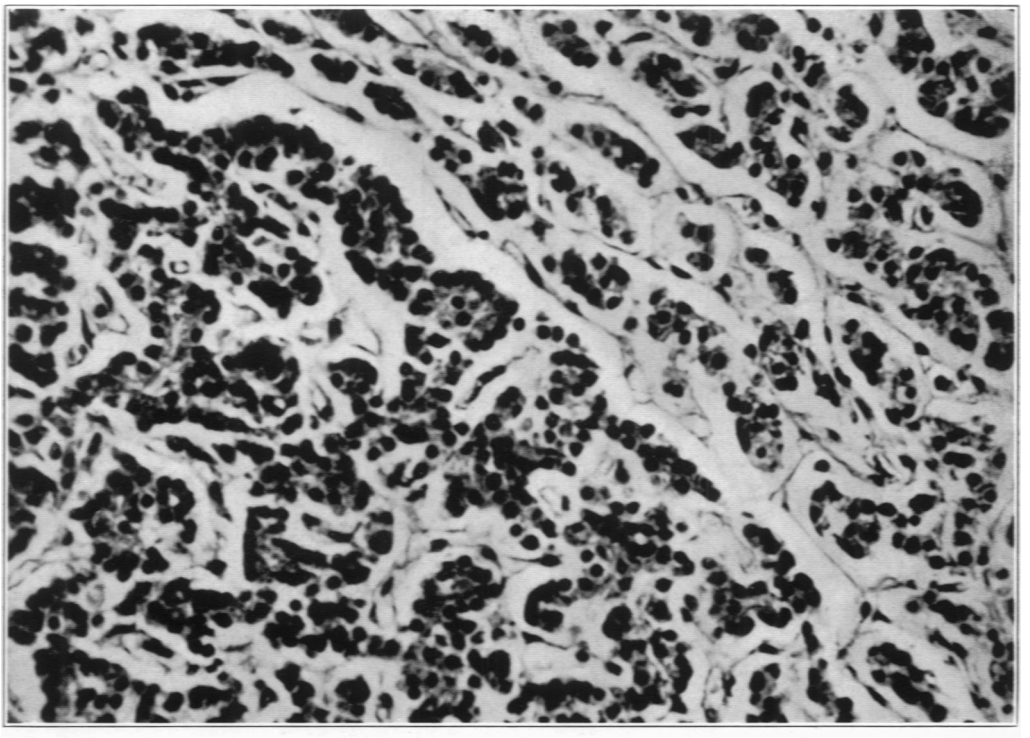

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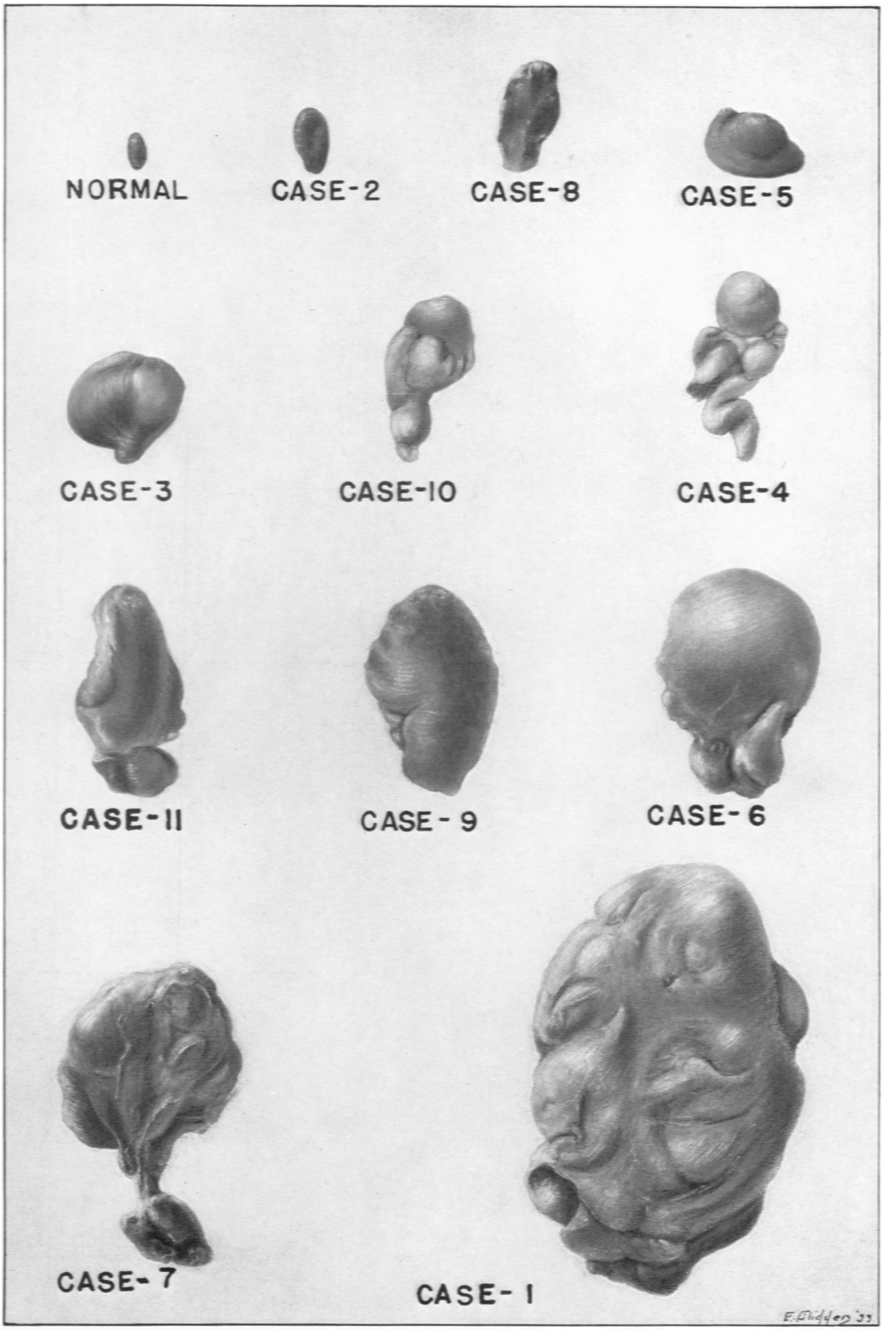
## Plate 5

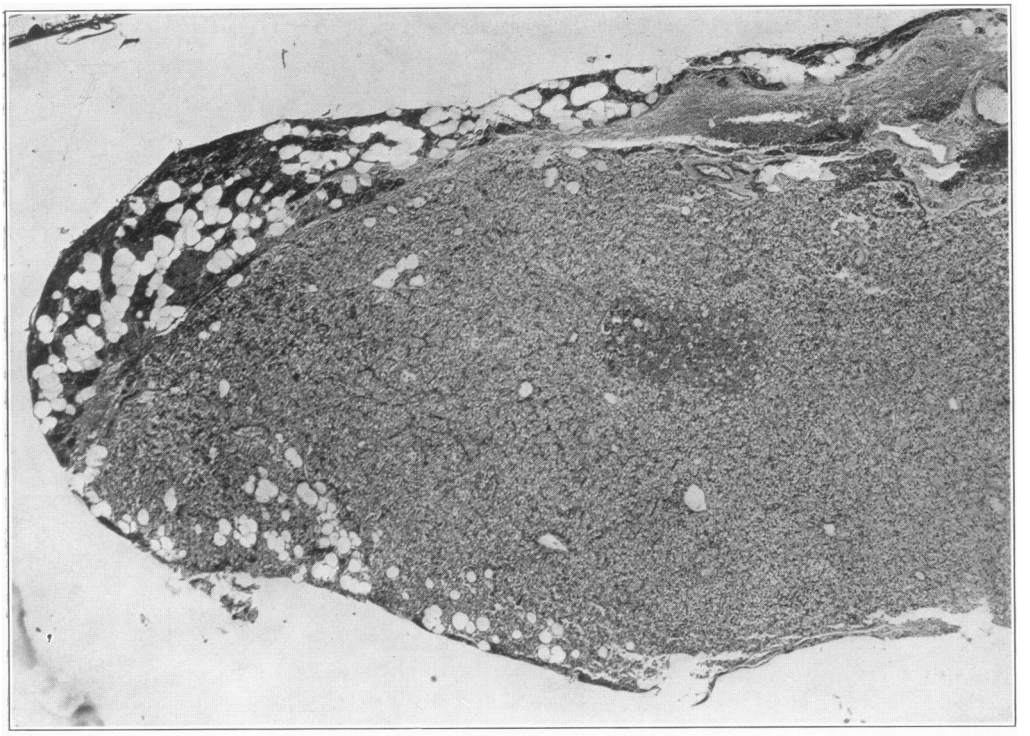
Fig. 14. An actual size drawing of the tumors removed from Cases 1 to 11. Note the variability in size and in shape.


NORMAL
CASE-2
CASE-8
CASE-5
CASE-3
CASE-10
CASE-4
CASE-11
CASE-9
CASE-6
CASE-7
CASE-1

## PLATE 6

FIG. 15. Case 2. A longitudinal section through almost the entire tumor showing a rim of normal parathyroid tissue surrounding a wasserhelle adenoma. In the latter is a localized group of transition oxyphil cells. × 15.

FIG. 16. A higher power of Fig. 15, showing the sharply demarcated wasserhelle cell. × 400.



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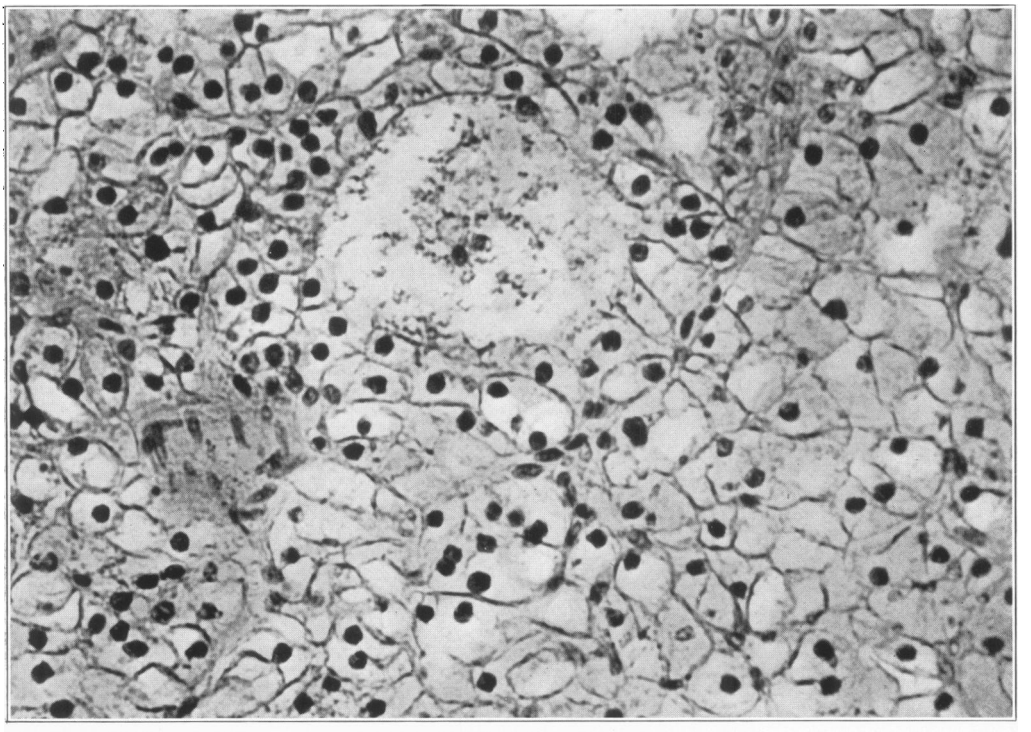

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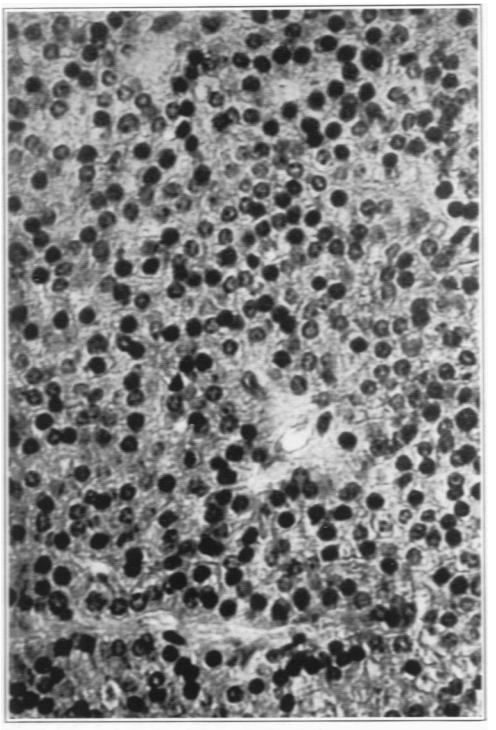
## Plate 7

Fig. 17. Case 6. An example of a chief cell tumor showing the enlarged chief cell with its poorly outlined cell margin, its large hyperchromatic nucleus and its faintly acidophilic cytoplasm. Note the increased vascularity, the compact grouping of the cells and the absence of fat. × 400.

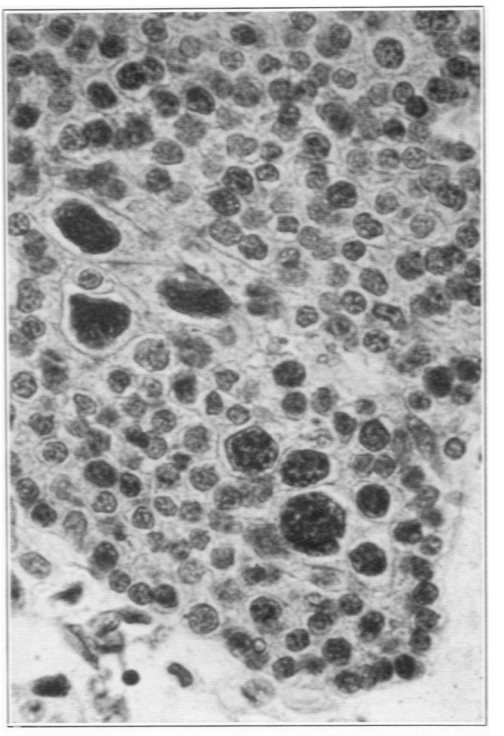
Fig. 18. Case 11. A chief cell tumor with numerous greatly enlarged cells and giant hyperchromatic nuclei. Even the smaller cells are well above the normal in size. × 400.

Fig. 19. Case 3. An example of a transition wasserhelle cell tumor. About the nuclei clear halos of varying width can be seen. Occasionally they extend to the cell margins. The cells closely continguous to the stroma are barely discernible. × 400.

Fig. 20. Case 19. An example of a transition oxyphil cell tumor. These cells show transition stages from the chief to the pale oxyphil cell. Note the granular abundant cytoplasm and the pseudoglandular arrangement. × 400.



17



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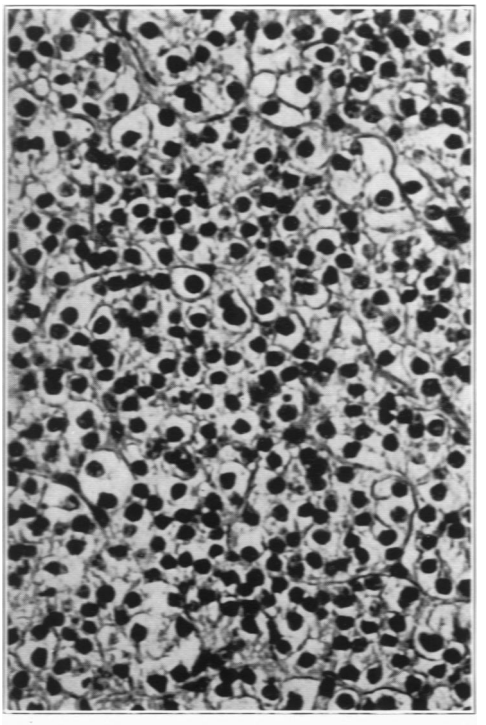

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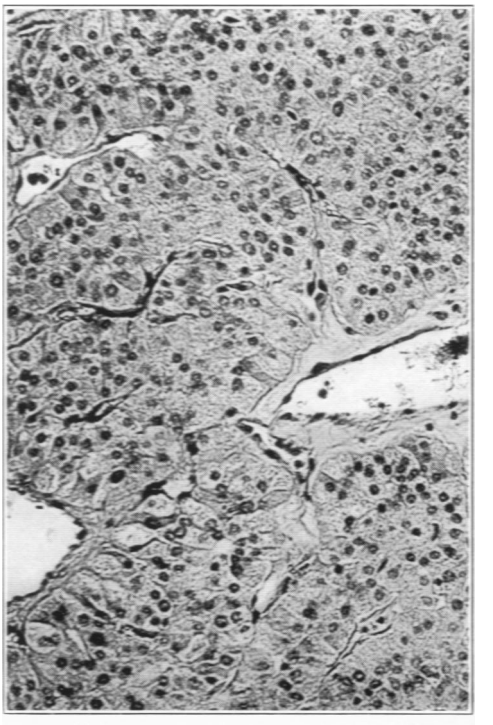

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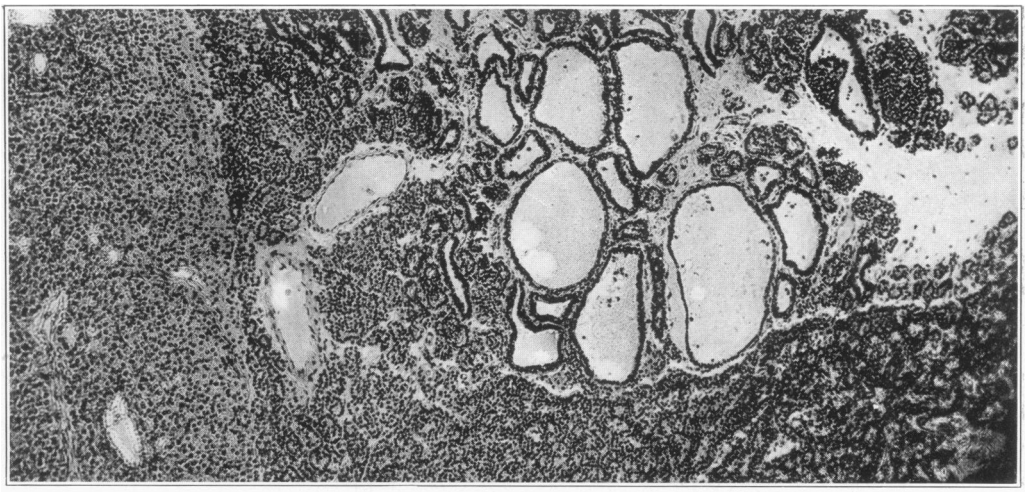
## Plate 8

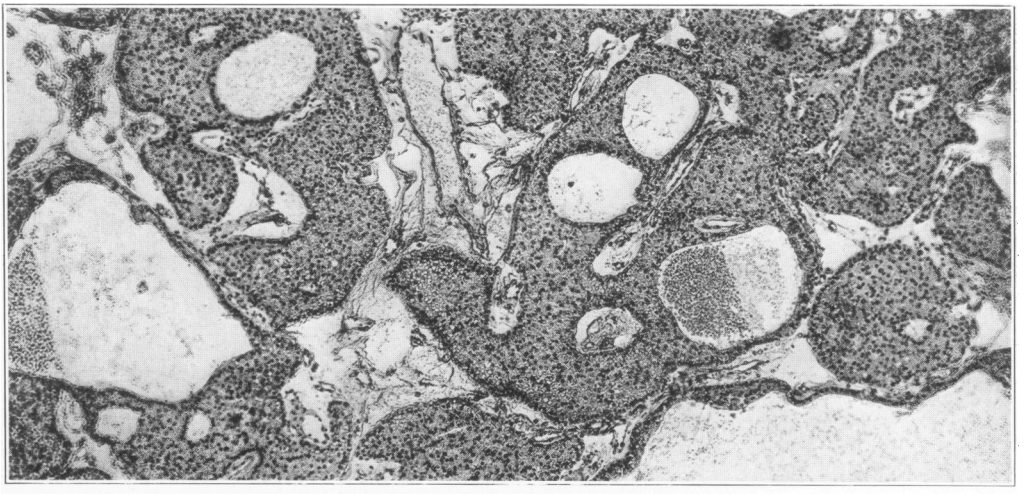
Fig. 21. Case 4. An example of a glandular and cystic chief cell tumor. In addition to the glandular area in the upper part of the photomicrograph note the pale oxyphil cells on the left and the chief cells below. × 50.

Fig. 22. Case 13. Another example of the glandular and cystic type. In this case the spaces are not so close to each other and are larger. Note the presence of red blood cells in some of the glands. × 50.

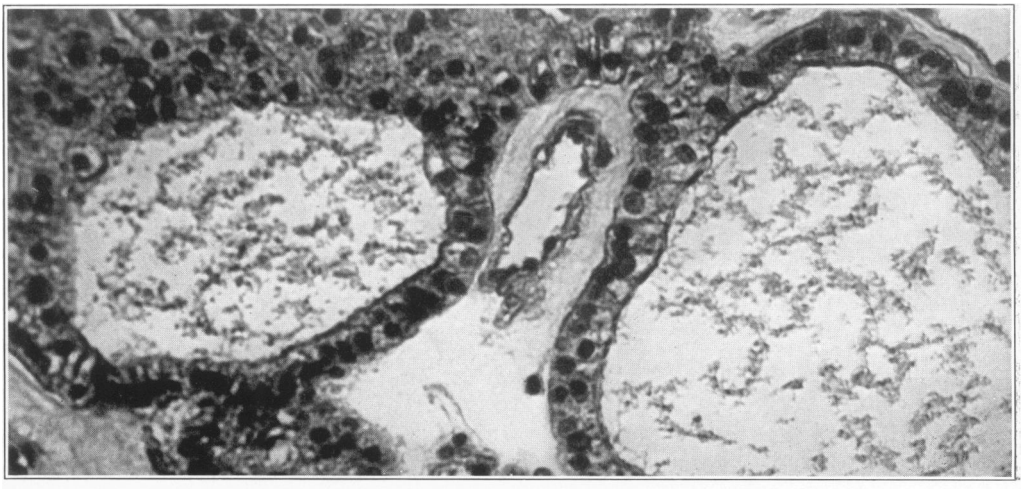
Fig. 23. Case 13. A higher power of Fig. 22, showing the chief cells lining these spaces. × 400.



21



22



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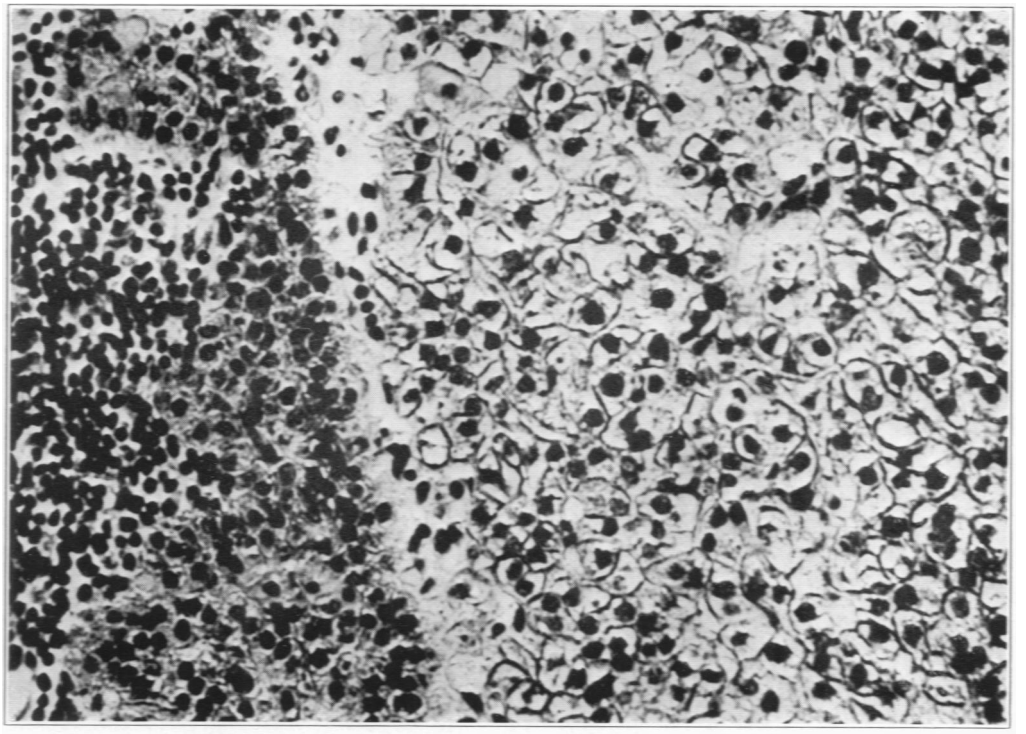
## PLATE 9

FIG. 24. An example of a focal wasserhelle cell tumor showing the large islands of waterclear cells, surrounded by moderately enlarged chief cells. × 400.

FIGS. 25 and 26. Case 20. An example of multiple chief cell tumors showing the dissimilarity of two tumors in the same case. One is definitely glandular; the other belongs to the transition wasserhelle cell type and is nonglandular. × 100.



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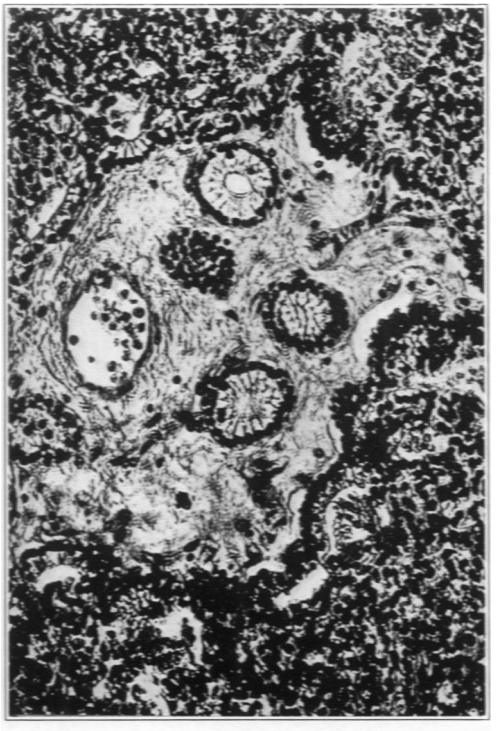

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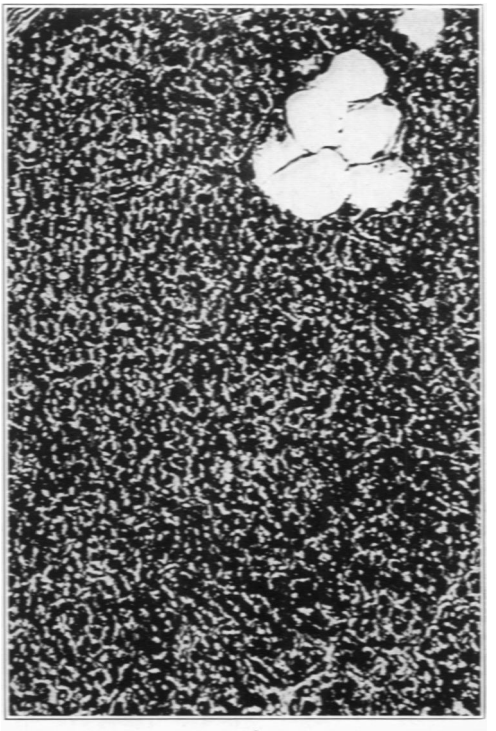

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