TUMORS OF THE PARATHYROID GLANDS

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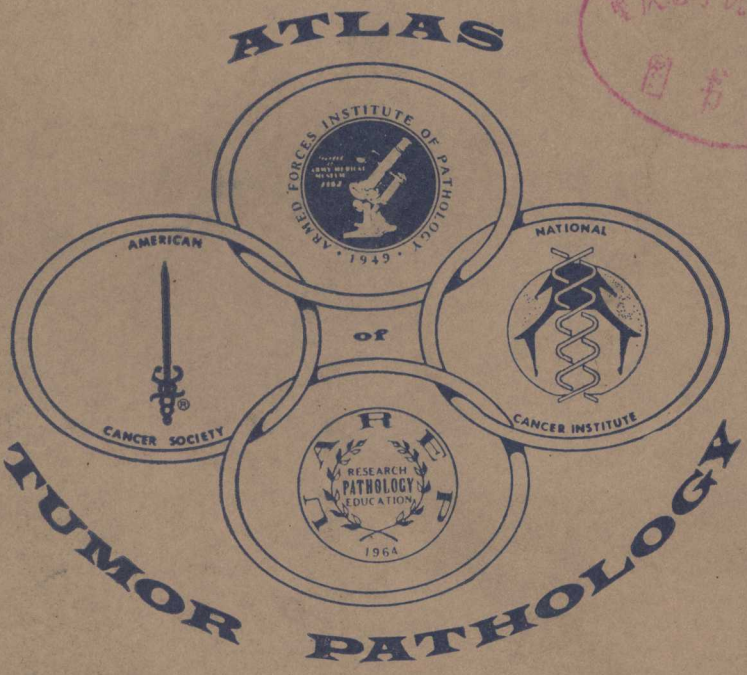

ATLAS OF TUMOR PATHOLOGY

Second Series
Fascicle 14

TUMORS OF THE PARATHYROID GLANDS

by

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ATLAS OF TUMOR PATHOLOGY

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EDITORS' NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences–National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was made by the press at the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final fascicle of the first Atlas, the National Academy of Sciences–National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout the rest of this new series, the term chosen for the World Health Organization's series "International Histological Classification of Tumours" (when available) is shown by an asterisk if it corresponds to the authors' choice, or as the first synonym in bold print if it differs from the authors' heading. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information when indicated for a better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index will be included in each fascicle.

It is the hope of the Editors, past and present, the Editorial Advisory Committees, past and present, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will always be appreciated.

William H. Hartmann, M. D.
William R. Cowan, M. D.

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Finally, we wish to thank the following for having generously contributed microscopic slides, photographs, photomicrographs, or charts for use in this fascicle: Dr. A. von Albertini and Dr. F. Koller, Zurich, Switzerland; Dr. F. M. Vellios, Dallas, Texas; Dr. C-A. Wang, Boston, Massachusetts; and Dr. M. Wolman, Tel Aviv, Israel.

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TUMORS OF THE PARATHYROID GLANDS

Contents

	Page No.
Introduction	1
History	1
Normal Parathyroid Gland	3
Embryology	3
Gross Anatomy	6
Microscopic Anatomy	6
Ultrastructure	11
Blood Supply	13
Primary Hyperparathyroidism	21
Adenoma	29
Lipoadenoma	52
Chief-cell Hyperplasia	54
Clear-cell Hyperplasia	67
Carcinoma	74
Therapy	79
Malignant Nonparathyroid Tumors Associated with Hypercalcemia and Hypophosphatemia	82
Secondary Hyperparathyroidism	83
Tertiary Hyperparathyroidism	89
Nonfunctional Enlargement	90
Oxyphil Adenoma	90
Primary Carcinoma	90
Metastatic Carcinoma	90
Parathyroid Cysts	91
Index	93

TUMORS OF THE PARATHYROID GLANDS

INTRODUCTION

The tumors referred to in the title of this Fascicle are generally those that cause enlargement of the parathyroid glands. The discussion, therefore, concerns lesions that produce primary hyperparathyroidism—adenomas, hyperplasias, and carcinomas. In addition, other functioning and nonfunctioning lesions of the parathyroid glands will be discussed briefly.

Since publication of the first Fascicle on this subject in 1952, there have been numerous advances in the understanding of the ultrastructure, biochemistry, and physiology of normal and abnormal parathyroid glands. The increased clinical recognition of hyperparathyroidism and the routine determination of the serum calcium level in the multiphasic screening of apparently healthy persons have led to an earlier diagnosis of this disease, thus providing the pathologist with a large number of surgical specimens to broaden his experience. A new entity, primary chief-cell hyperplasia, involving all four parathyroid glands has been recognized (Cope et al.). The differentiation between adenoma and the rare carcinoma of the parathyroid gland has been refined.

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HISTORY

The parathyroid glands were first described in the rhinoceros in 1862 by Owen. Virchow, in 1863, was the first to describe this gland in man, but it was Sandström, in 1880, who presented the first relatively complete comparative description of the gland and gave it the present name. Subsequently, there have been numerous comparative studies of the parathyroid glands in various species. In 1903, Askanazy reported a parathyroid tumor (an adenoma) found at autopsy in a patient with von Recklinghausen's disease (osteitis fibrosa cystica generalisata). Since that time, other authors have made the connection between the parathyroid tumor and the bone disease, but it remained for Mandl, a Viennese surgeon, in 1925, to remove a parathyroid tumor from a living patient with von Recklinghausen's disease.

In the United States, the first patient operated on for primary hyperparathyroidism, Captain Charles Martell, required six neck explorations, the first in 1926 at the Massachusetts General Hospital, before the tumor was finally discovered in the mediastinum in 1932. The first successful parathyroid exploration in the United States was at the Barnes Hospital, St. Louis, in 1929 (Barr and Bulger). Albright and his co-workers, in 1934, recognized the entity of clear-cell hyperplasia of the parathyroid glands. Hall and Chaffin, in 1935, reported the first carcinoma of a parathyroid gland. Castleman and Wilens described the histologic changes in the secondary parathyroid hyperplasia that occurs as a result of chronic renal disease.

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NORMAL PARATHYROID GLAND

Knowledge of the embryologic development and the normal anatomic variations of the parathyroid gland is necessary to recognize and understand pathologic alterations.

EMBRYOLOGY

The human parathyroid glands are first recognizable in the 8 to 9 mm. embryo as bilateral localized proliferations arising from the third and fourth branchial pouches. When the third pouch separates from the pharynx, parathyroid III* forms part of a bilobed body with the thymus III, and, as the heart descends into the thorax, it pulls thymus III and parathyroid III caudally with it†. In the 18 mm. embryo, when parathyroid III is approximately at the level of the lower pole of the thyroid gland, it usually separates from the thymus gland and remains near the lower pole of the thyroid gland as the lower parathyroid gland. However, one or both parathyroid IIIs may remain attached to the thymus gland and come to lie in the lower neck or the anterior mediastinum as far caudad as the pericardium, or even in the posterior mediastinum. If parathyroid III separates prematurely from the thymus gland, its final position may even be cephalad to the thyroid gland and parathyroid IV. In recent studies of the locations of normal parathyroid glands, Wang found that the lower gland was on the anterior or posterolateral surface of the thyroid gland in 42 percent of the cases (fig. 1); 39 percent were in the lower neck underneath the capsule of the thymic tongue, 15 percent were in the neck lateral to the lower pole of the thyroid gland, 2 percent were in the mediastinal thymic tissue, and the remaining 2 percent were at the carotid bifurcation above the upper pole of the thyroid gland or lateral to the midportion of the gland.

Parathyroid IV forms a bilobed complex with the ultimobranchial or postbranchial body (lateral thyroid), the gland associated with the calcitonin-secreting C cells. As the ultimobranchial body joins the lateral lobes of the thyroid gland, parathyroid IV separates from it and finds its adult position as the upper gland, near the point where the medial thyroid artery crosses the recurrent laryngeal nerve at the cricothyroid junction posteriorly. Since parathyroid IV (upper gland) is more medial and closely associated with the midline structures than parathyroid III (lower gland), the former has more movement in a cephalad direction and is more constant in position, although its position may vary in the dorsoventral plane with respect to the nerve and artery. In Wang's series, 77 percent of the upper

.....

*Parathyroid III refers to the parathyroid glands derived from the third branchial pouch, and parathyroid IV to the glands derived from the fourth pouch. Unless otherwise noted, the glands from each pouch develop approximately symmetrically, and, therefore, the singular is used.

†Although embryologic usage refers to structures rising and descending, the relative alterations in location of structures are due in large part to differential growth rates of adjacent organs.

glands were found at the cricothyroid junction (fig. 2), 22 percent were behind the upper pole of the thyroid gland, invariably underneath the surgical capsule of the thyroid (also known as the pretracheal lamina of the cervical fascial sheath), and 1 percent were in the midline behind the pharyngoesophageal junction.

Rarely, either parathyroid gland may remain in the pharyngeal wall or move more

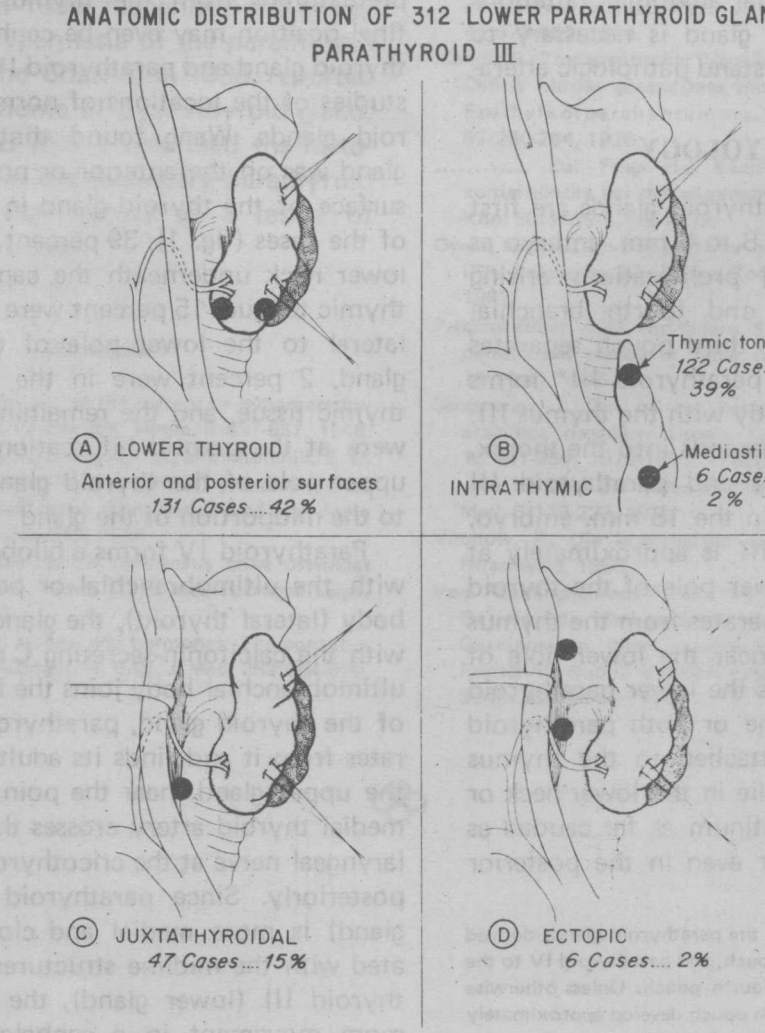

Figure 1
NORMAL PARATHYROID GLAND
Anatomic distribution of 312 normal lower parathyroid glands. (Fig. 2 from Wang, C-A. The anatomic basis of parathyroid surgery. Ann. Surg. 183:271-275, 1976.)

ventrally to lie in the esophagotracheal groove or behind the esophagus. The glands tend to be bilaterally symmetrical in location. Although the number of parathyroid glands has been reported to vary between two and eight, in the most careful studies the finding of less than four glands in either the embryo or the adult is rare. Supernumerary glands, which have been reported in 2 to 6.5 percent of adults, probably

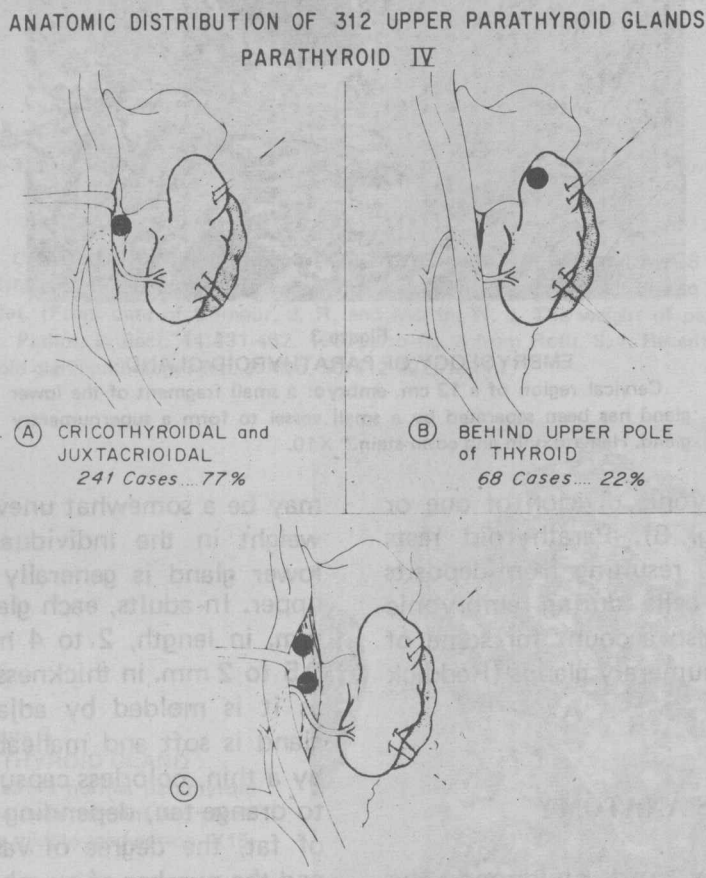

Figure 2
NORMAL PARATHYROID GLAND
Anatomic distribution of 312 normal upper parathyroid glands. (Fig. 1 from Wang, C-A. The anatomic basis of parathyroid surgery. Ann. Surg. 183:271-275, 1976.)

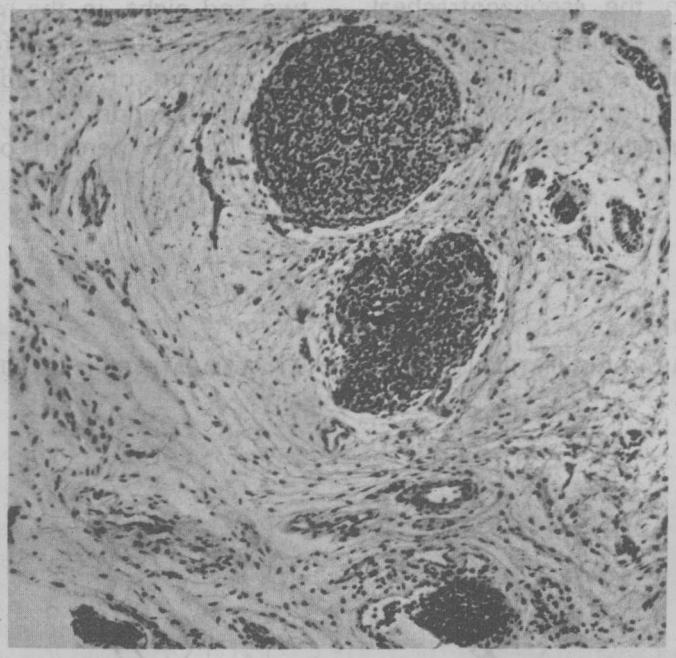

Figure 3
EMBRYOLOGY OF PARATHYROID GLAND
Cervical region of a 12 cm. embryo: a small fragment of the lower gland has been separated by a small vessel to form a supernumerary gland. Hematoxylin and eosin stain.* X10.

result from embryonic division of one or more glands (fig. 3). Parathyroid rests (parathyromatosis) resulting from deposits of parathyroid cells during embryonic migration could also account for some of the smaller supernumerary glands (Reddick et al.).

GROSS ANATOMY

From infancy and childhood, the growth of the parathyroid gland continues until the late third or early fourth decade, when the weight of the total parathyroid gland levels off at 120 ± 3.5 mg. in men and 142 ± 5.2 mg. in women (fig. 4). There may be a somewhat uneven distribution of weight in the individual glands, and the lower gland is generally heavier than the upper. In adults, each gland is from 3 to 6 mm. in length, 2 to 4 mm. in width, and 0.5 to 2 mm. in thickness; it varies in shape as it is molded by adjacent tissues. The gland is soft and malleable and is covered by a thin, colorless capsule. It is yellow-tan to orange-tan, depending upon the amount of fat, the degree of vascular congestion, and the number of oxyphil cells.

MICROSCOPIC ANATOMY

The adult gland is composed of chief and oxyphil cells and a stroma largely consisting of fat cells (fig. 5). The chief cell is polyhedral and poorly outlined and 6 to 8

*Throughout the fascicle where the stain is not so designated, hematoxylin and eosin stain has been used.

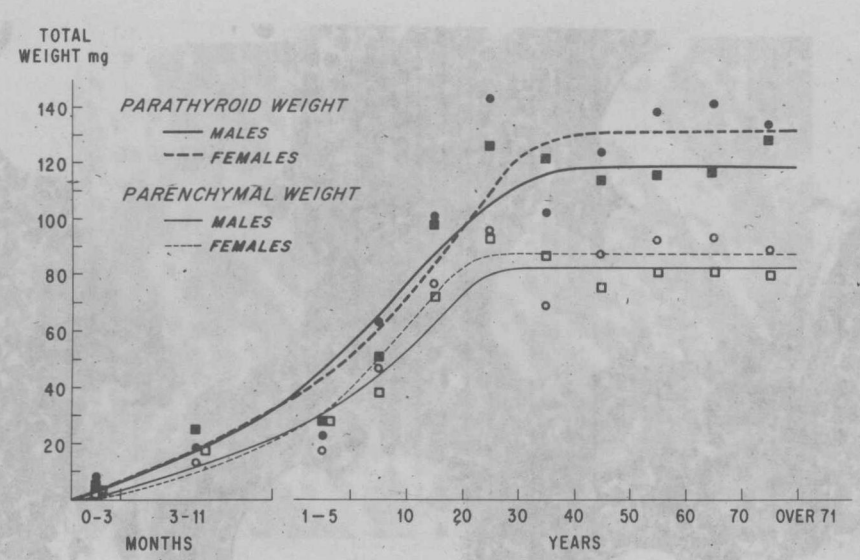

Figure 4

CHART DEMONSTRATING GROWTH OF PARATHYROID GLANDS

The difference in the total and parenchymal weight in older persons is due to increased stromal fat. (From data of Gilmour, J. R. and Martin, W. J. The weight of parathyroid glands. J. Pathol. & Bact. 44:431-462, 1937; also fig. 3 from Roth, S. I. Recent advances in parathyroid gland pathology. Am. J. Med. 50:612-622, 1971.)

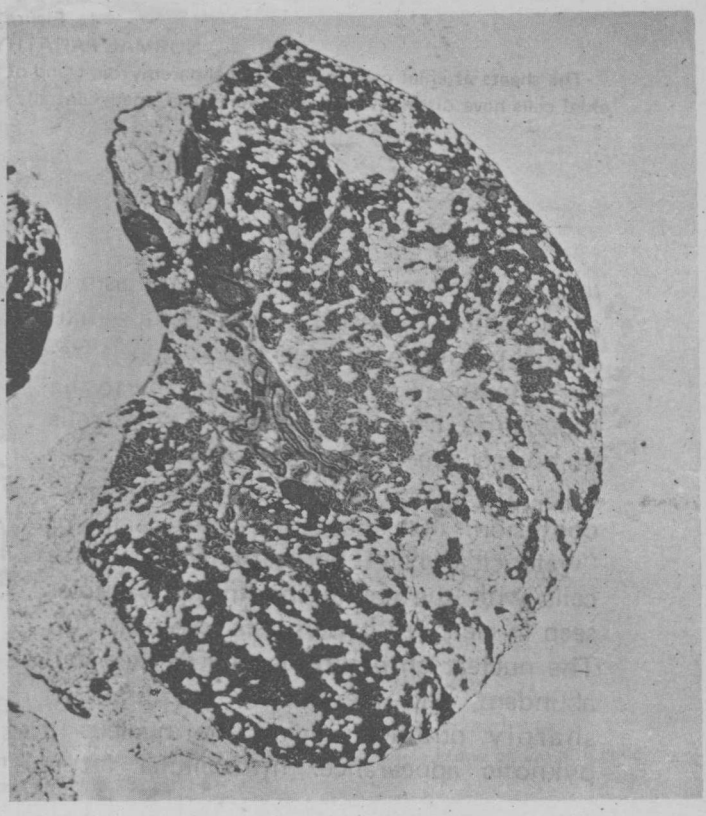

Figure 5

NORMAL PARATHYROID GLAND

Cross section of an entire normal parathyroid gland, demonstrating the usual amount and distribution of stromal fat in a middle-aged person. X15.

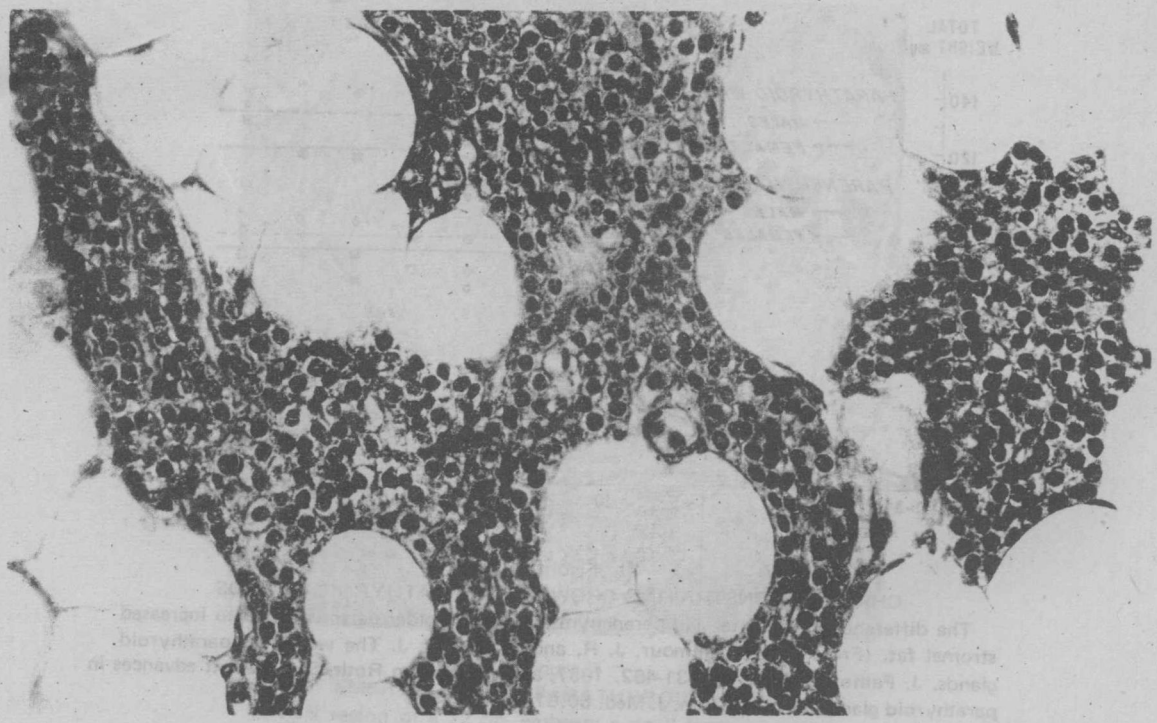

Figure 6
NORMAL PARATHYROID GLAND
The sheets of chief cells in this normal parathyroid gland of a middle-aged person are separated by mature fat cells. The chief cells have distinctive cell membranes and small, centrally located nuclei. X400. (Fig. 2 from Fascicle 15, First Series.)

μm. in diameter (fig. 6). The cytoplasm is amphophilic to slightly eosinophilic. Artifactual vacuolization due to fixation is frequently seen. Early workers referred to the vacuolated, often glycogen-rich, chief cells in normal glands and adenomas as "clear cells" (see page 36). We suggest, to avoid confusion, that the terms "clear cell" or "water-clear cell" be restricted to those cells with the membrane limited vacuoles seen in clear-cell hyperplasia (see page 70). The nuclear chromatin is well defined and abundant, and the nuclear membrane is sharply outlined, giving the nucleus a pyknotic appearance. Intracellular fat is present in 70 to 80 percent of the normal chief cells of a euparathyroid person (fig. 7).

Near the time of puberty, the oxyphil cells appear, at first singly and then in groups, presumably representing clones. An occasional oxyphil cell has been seen in childhood. They increase in number with advancing age, often forming large islands and nodules. After 60 years of age, they may occupy a large proportion of the gland, forming large single nodules (fig. 8) that may be incorrectly interpreted as neoplastic. The oxyphil cells are 8 to 12 μm. in diameter, with well demarcated cell mem-

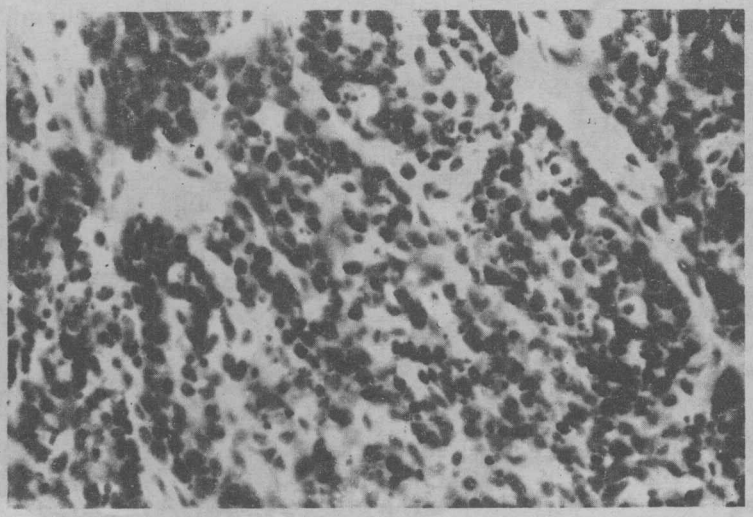

Figure 7
NORMAL PARATHYROID GLAND
Normal parathyroid gland, with intracellular fat droplets in 70 to 80 percent of the chief cells. Sudan IV and toluidine blue stain. X300.

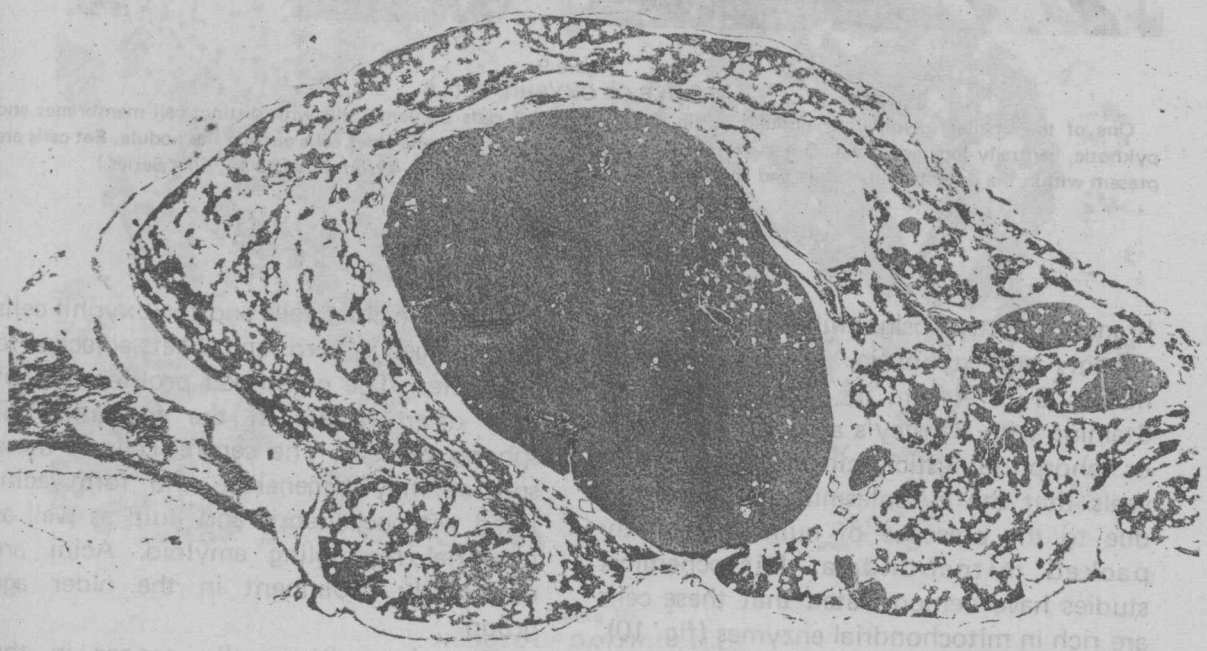

Figure 8
PARATHYROID GLAND
(Figures 8 and 9 from same case)
Cross section of an entire parathyroid gland from an elderly person, demonstrating a large single island of oxyphil cells and several smaller oxyphil cell nodules. X25. (Fig. 3 from Fascicle 15, First Series.)

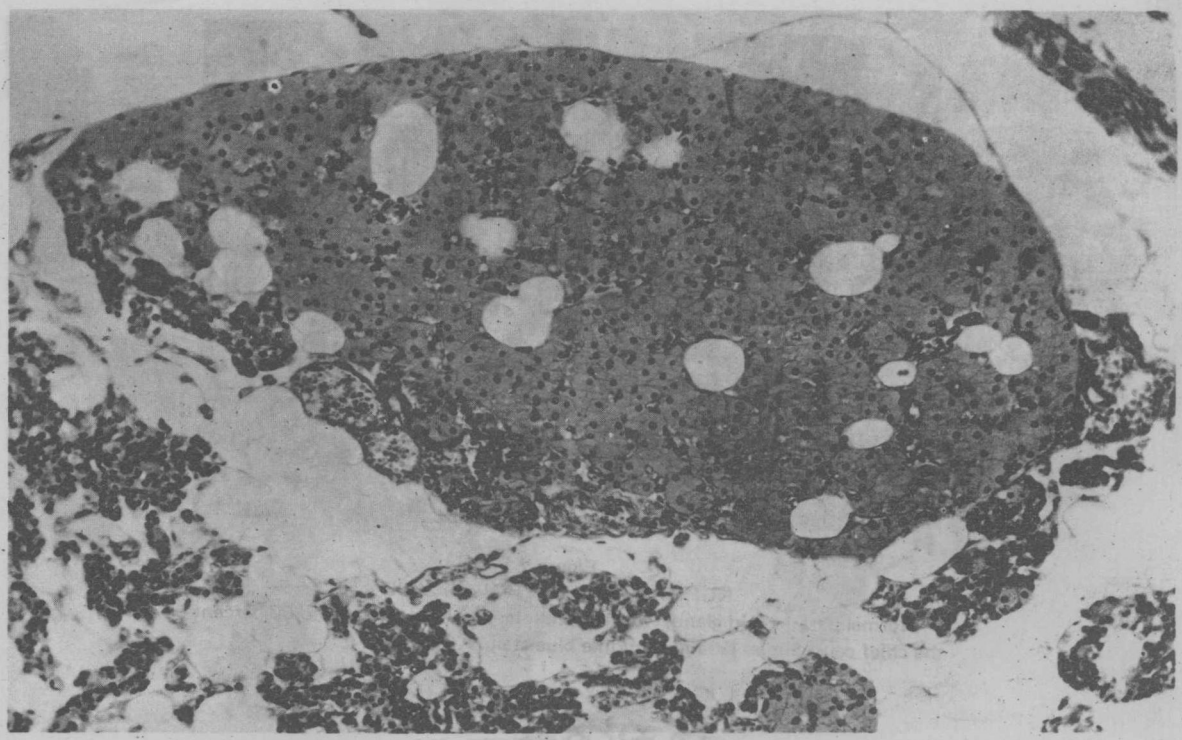

Figure 9
NODULE OF OXYPHIL CELLS

One of the smaller oxyphil cell nodules in fig. 8. The oxyphil cells are large cells with distinct cell membranes and pyknotic, centrally located nuclei. Other oxyphil cells are intermixed with the chief cells outside the nodule. Fat cells are present within the oxyphil cell nodule and among the stromal cells. X165. (Fig. 4 from Fascicle 15, First Series.)

branes, brightly eosinophilic granular cytoplasm, and pyknotic, centrally located nuclei, 3 to 4 μm. in diameter (fig. 9). Staining with Bensley's acid aniline-fuchsin or phosphotungstic acid-hematoxylin reveals that the cytoplasmic eosinophilia is due to the presence of numerous tightly packed mitochondria. Histochemical studies have demonstrated that these cells are rich in mitochondrial enzymes (fig. 10), although biochemical studies have indicated that the mitochondria may be defective. A transitional (pale, light) oxyphil cell with less intense cytoplasmic eosinophilia is a variant of the oxyphil cell.

Both the chief cells and the oxyphil cells are arranged in cords and sheets adjacent to capillaries. The continued proliferation of cells often results in the formation of spheres of cells. The central cells in these spheres may degenerate and form acini filled with cell debris and fluid as well as material resembling amyloid. Acini are especially prominent in the older age group.

The fat cells usually appear in the stroma near the time of puberty, although occasional fat cells are seen in younger children. The number of fat cells increases until the age of about 40 years and then