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Hurthle cell tumor of the thyroid gland : a review of thirteen cases

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HURTHLE CELL TUMOR OF THE THYROID GLAND
A REVIEW OF THIRTEEN CASES

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INTRODUCTION

Hurthle cell tumors occupy a controversial position within the realm of pathologic changes in the thyroid gland. Generally considered to be a relatively rare tumor, the incidence attributed to this entity ranges widely however from author to author. Goldenberg (1) asserts that 30% of all malignant thyroid tumors are of the Hurthle cell type; while others, such as Chesky, et al. (2), Warren (3), and Sedgewick (4), state that this tumor accounts for less than 3% of thyroid malignancies. Although reference is made above to malignant thyroid tumors, the interpretation of the significance of the Hurthle cell, particularly in regard to its benign or malignant nature, is far from uniform. In a like manner, or as a consequence, recommended treatment reflects an equally wide divergence of opinion. In spite of differences noted in the broader aspects of this problem, the histologic characteristics of the cells comprising these tumors seem well established. The "Hurthle cell" is a large cell (15 -30 microns diameter) with pale staining cytoplasm within which are seen many eosinophilic granules. The large number and relatively small size of these granules give the cytoplasm a cloudy appearance under low power. The nuclei are often vesicular, although occasionally varying degrees of pyknocity are seen, and are usually eccentrically placed. Conspicuous nucleoli are frequently noted. More often cell outlines are distinct,

although at times definite individuality of cells is lost. Comparison has often been made between the appearance of the Hurthle cells and the cells of the liver and adrenal gland. Hurthle cells may be arranged in trabeculations, alveoli (small follicles), large follicles or papillary formations, although the latter is rare according to Frazell and Duffy (5).

It is the purpose of this paper to present data accumulated from thirteen new cases of Hurthle cell tumor, and to review the theories of the origin and significance of the distinctive cells which compose them. For it is such an understanding upon which depend rational therapy and the ability to make sound prognosis.

PRESENTATION OF DATA

In this study, thirteen new cases of Hurthle cell tumors were reviewed. Six of these cases were studied from hospital records. In addition pathologic specimens from seven other patients operated elsewhere were reviewed. Follow-up studies on twelve of the thirteen patients were successful.

AGE AND SEX INCIDENCE

The sex incidence, as noted here, again affirms the observation frequently made in the past that females predominate conspicuously in this condition. In this series, three (23%) of the patients were male and ten (77%) were female. These figures compare rather closely with Morrow (6) who found an incidence of 74% in females. Chesky, et al. (2) state that their series was composed of 96% female and 4% male. Frazell and Duffy (5) note 67% female and 33% male in

their review of forty cases. Goldenberg's figures indicate that 86% were female and 14% were male.(1)

Age range of the patients in this group was 28 to 70 years. The average age was 52.3 years, while the median was 58 years. Ninety-two percent of these patients were over age 40, an observation noted by Goldenberg in 82% (1). Frazell and Duffy (5), and Chesky, et al. (2), found that the median and average ages, respectively, were 50 years.

CLINICAL SYMPTOMS AND SIGNS

A mass in the neck was present in all cases and was the chief symptom in all but one case. The duration of the mass varied from one week to 25 years. Forty-six percent of these patients had had the mass for over four years. Thirty percent were aware of the mass for one year or less. Sixty-one percent of the patients stated that the mass had seemed to enlarge rather rapidly within a year prior to admission.

In one case the initial symptoms and chief complaints were hoarseness and dysphagia, of which the patient was aware two weeks prior to noting the presence of a mass in the neck. Altogether three patients (23%) complained of persistent dysphagia and hoarseness, although one of these first noted hoarseness immediately following previous thyroid surgery.

Only one case revealed a history or laboratory evidence of thyrotoxicosis. This represents 8% of all cases, which is a considerably lower figure than the 36% rate of toxic

patients seen by Chesky, et al. (2), the 23% noted by Goldenberg (1), or the 40% reported by Morrow.(6)

Preoperatively, nine of these patients (69%) were diagnosed as non-toxic solitary adenomas. One patient was believed to have a non-toxic nodular goiter. Three patients (23%) were thought to have a carcinoma preoperatively, Of these latter three, one had been operated twice previously elsewhere for thyroid carcinoma and local recurrence--presumably Hurthle cell carcinoma in each instance. A second patient had a preoperative diagnosis of carcinoma, for reasons unknown at this time. The third patient had a palpable lymph node which was biopsied, disclosing metastatic tumor, and because of concomitant hyperthyroidism, poor risk patient, metastases to regional nodes, a trial of radiation therapy was instituted prior to further resection.

TREATMENT

Of those patients with preoperative diagnosis of solitary adenoma, four were treated by complete lobectomy on the involved side; three had subtotal lobectomies, and two had partial lobectomies. One patient was believed to have involvement of both lobes at time of surgery, andwas treated by means of subtotal lobectomy on one lobe and partial lobectomy on the other. The patient with "nodular goiter" received a total thyroidectomy.

Of those patients with preoperative diagnosis of cancer,

one patient, previously unresected, received total thyroidectomy but no neck dissection. A third resection for local recurrence was done on another patient twice resected previously. At time of surgery, it was seen that marked local involvement of ribbon musculature and carotid sheath on one side had occurred. Palliative resection was attempted, but tumor involving the carotid sheath was left behind. The third patient received a node biopsy initially, following which three separate courses of treatment with external radiation were given. In addition, three courses of I^{131} were administered, preceded initially by propylthiouracil therapy. Five months after biopsy had been done, local resection of the cervical metastasis was done because of progressive enlargement. At the time of surgery the lobe on the involved side was stated to be well controlled by irradiation and was left intact. Two more courses of external radiation and I^{131} were conducted postoperatively.

PATHOLOGY

Description of gross surgical specimens were available in six of the thirteen cases. The tumor masses ranged in size from several modules of 1/2 to 1-1/2 cm in diameter to solitary tumors measuring 7 cm in diameter. The weight varied from 10 grams to 235 grams. Two specimens were uniformly solid and fleshy in appearance on cut section, whereas four were noted to show varying degrees ofcystic degeneration. Two of these cystic specimens were seen to have only a single small polypoid mass of solid tumor adherent to the cyst wall.

Four of these specimens, all from cases diagnosedat surgery as solitary adenomas were said to be well encapsulated. Two other cases were said to be partially encapsulated, one being a "solitary adenoma", and the other a recurrent carcinoma.

Microscopically, all types of cellular arrangement previously described in the literature were observed. Four tumors (31%) were composed of Hurthle cells arranged in trabeculations, alveoli, and large follicles. Three specimens (23%) consisted predominantly of large trabeculations with minimal amounts of alveolar formation. Three cases (23%) showed predominantly alveolar formation with a lesser degree of trabeculation. Two cases (16%) were uniformly trabeculated, and one case (8%) showed a mixture of trabecular pattern and papillary formation with lesser amounts of alveoli.

Goldenberg (1) noted 41% trabeculated, 32% alveolar, 9% papillary and 18% mixed. Frazell and Duffy (5) agree that papillary types are rare.

Vascular invasion was observed in three cases, and in all of these, capsular structure was infiltrated or eroded by Hurthle cells. In one of these, cellular arrangement was observed to be uniformly trabeculated with marked variation in cell size and nuclear size and density. At time of operation marked involvement of local structures was noted, and subsequently (2-1/2 years later) osseous metastasis became apparent, and the patient expired shortly thereafter. The

other two cases had tumors composed predominantly of trabeculated pattern and mixed arrangement respectively. These cases clinically and at time of surgery were believed to be solitary adenomas, and have as yet shown no evidence of bony or other distant metastasis. One of these, however, has experienced recurrent local enlargement seven years after her second surgical resection, and twelve years after initial surgery.

A fourth case, in which arrangement of cells was noted to be predominantly alveolar, and in which no evidence of capsular erosion or vascular invasion was detected, developed metastasis to the tenth dorsal vertebra seven years following her resection. The patient, however, is still living and active, two years following this metastasis.

FOLLOW-UP

Of the thirteen patients included in this review, one developed marked local recurrence and metastasis to the spine with resultant paralysis distally, 26 months after his third resection. He expired 29 months after his third surgical procedure, which represented 11 years and 4 months after the diagnosis was first made. Three patients are living, with local evidence of recurrence, one of whom was resected a second time five years and ten months after her first procedure. Still another patient is living and active nine years following surgery, and two years following the development

of metastasis to the ninth dorsal vertebra.

Seven patients are living, with no evidence of disease from eight months to six years following surgery.

One patient has been lost to follow-up study.

Died with Disease	8%
Living with Disease	23%
Living and Well	61%
Unknown	8%

PT.	AGE	SEX	CLINICAL SUMMARY	CLINICAL DIAGNOSIS	TREATMENT	PATHOLOGY		FOLLOW-UP
						GROSS	MICROSCOPIC	
R.B.	70	M	Multi-nodular mass, right side of neck over 9 yrs. Twice operated (9 & 4 yrs p.t.a). Hoarse since 2nd operatin. Present mass recurred 3 yrs p.t.a. Radiation (amount?) 3 yrs. p.t.a. No toxic symptoms.	Recurrent carcinoma	Resection of recurrent tumor mass. Residual left in rt. carotid sheath & larynx. Post-op radiation	150 gm. Partially encap. Cut sec.: soft, yellow-pink. Cystic degeneration.	Trabeculated capsular infiltration, vascular invasion. Orderly, anaplastic appearance. Cells vary in size, with variation in size & density of nucleus.	Expired 29 mo. post-op. with metases to spine & distal paralysis.
D.J.	28	F	Hoarseness & dysphagia 4 weeks p.t.a. Mass in left neck 3 weeks p.t.a. No toxicity.	Solitary adenoma.	Left partial lobectomy.	3 cm diameter. Well encapsulated. Cut section: Dark, gray-red. Bulges.	Sm. & Lg. follicles with considerable colloid production. Frequent nests of Huerthe cells. Marked lymphocytic infilt. of surrounding "normal" tissue & capsule. No cap. erosion or vascular invasion.	L & W 6 years
E.S.	60	F	Progressive swelling ant. neck--8 mos. 4x6 cm mass rt. ant. neck, firm, not fixed. Moves with swallowing. Sl. enlargement lt. side. BMR 1 plus; minus 2.	Solitary adenoma.	Right sub-total resection.	1st spec: 7x5x5.5 cm Well encapsulated. Cut section: Multiple nodules, tan-yellow or hemorrhagic.	1st spec.: Well encapsulated. Fairly well diff. but little acinar formation. No vascular invasion.	Resected for recurrence 5 yrs 10 mo. later in cerv. nodes. No other evidence of metastasis. Living with recurrence 6 yrs. after diagnosis.

SUMMARY OF SIX IN-PATIENTS.

PT.	AGE	SEX	CLINICAL SUMMARY	CLINICAL DIAGNOSIS	TREATMENT	PATHOLOGY		FOLLOW-UP
						GROSS	MICROSCOPIC	
M.P.	50	F	Lump in neck 1 yr. Enlargement 2 months p.t.a. No toxic symptoms.	Solitary adenoma.	Right partial lobectomy	5 cm diameter. Well encapsulated. Cut section: cystic degeneration with reddish-brown tissue & hemorrhage	Papillary & Trabeculated type with minimal sm.foll. formation. No lymphocyte infiltration. Capsule intact & no vessel invasion.	L & W 3½ yrs. after diagnosis. BMR 5.
J.E.	40	M	Lump in rt. neck for 4 yrs. with prog. enlargement. No choking. No thyrotoxicosis.	Solitary adenoma.	Subtotal rt. lobe. Partial lt. Lobe.	2 spec. totaling 93 gm. Partially encapsulated. Cystic with polypoid mass, 3 cm with scattered smaller polypoid nodules.	Mixed trabeculated & sm. follicle type. Degeneration central-16 in large nests of H.C.s. No evidence of cap. erosion or vascular invasion. Colloid goiter outside encapsulated HCT.	Unknown.
L.T.	65	F	Goiter (rt. side), 25 yrs. with enlargement & toxicosis past 5 yrs. Palpable nodes rt. ant. neck.	CA of thyroid.	7 months: Biopsy & ext. radiation. Prophylthiouracil I^{131} I^{131} ext.x-ray. I^{131} ext.x-ray. Resection rt. cerv. mass. I^{131}-ext.x-ray. I^{131}	Well encapsulated. Cystic with plaque of solid tissue within cyst.	Sm. & lg. follicles & trabeculation. Several nodes show metastatic tumor cells.	Rt. lobe enlarged, no lung or osseus metastasis, cardiac failure (3/8/55), 2 yrs after diagnosis

SUMMARY OF SIX IN-PATIENTS.

PT.	AGE	SEX	CLINICAL SUMMARY	CLINICAL DIAGNOSES	TREATMENT	MICROSCOPIC PATHOLOGY	FOLLOW-UP
R.L.	48	M	Lump in left neck for 20 years. Enlarging for 6-8 months. No thyrotoxicosis.	Solitary adenoma.	Total left lobectomy.	Predominantly sm. follicle formation with moderate lymphocytic infiltration. Some trabeculation. No cap. erosion or vas. invasion.	L & W 11 months after diagnosis.
C.B.	58	F	Nodular goiter for 8 yrs. Enlarging past 4 months. No toxicity.	Nodular non-toxic goiter.	Total thyroidectomy.	Lg.mult.areas of sm. & lg. follicle formation. Rare trabecular nests. Marked lymphocytic infiltration with occasional germinal centers. No vas. invasion or cap. erosion.	L & W 8 months after diagnosis.
F.D.	52	F		CA of thyroid.	Thyroidectomy, total.	Small follicle with occ. nests of trabeculation. Lymphocytic infiltration. No. cap. erosion or vessel invasion.	Metastasis to T9 6 years 10 months after diagnosis. Living with no further recurrence, 8 years 9 months after diagnosis.
M.M.	44	F	Iodine for 9 years because of goiter. Enlarging within recent months. No toxicity. PX-3 to 4 cm mass left lobe.	Solitary adenoma.	Left lobectomy.	Sm. & lg. follicle formation. Trabeculation. Suggestion of cap. erosion. Vascular invasion.	L & W 11 months after diagnosis.
W.C.	62	F		Solitary adenoma.	Subtotal resection.	Predom.trabeculated with minimal sm.follicle formation. Indistinct cell boundaries. Capsular erosion and blood vessel invasion.	Local resection for recurrence 5 years after diag. Recurrent enlargement locally with no evidence of node or distant metastases 11 yrs 3 months after diagnosis.

SUMMARY OF SEVEN OUT-PATIENTS

PT.	AGE	SEX	CLINICAL SUMMARY	CLINICAL DIAGNOSIS	TREATMENT	MICROSCOPIC PATHOLOGY	FOLLOW-UP
R.D.	45	F	First noticed mass 1 wk. p.t.a. PX--Solitary mass, rt. lobe thyroid. No toxic signs.	Solitary adenoma.	Complete lobectomy, right.	Predominantly trabeculated with lesser degrees of sm. and large follicle formation. Capsule intact. No vessel invasion.	L & W 20 months after diagnosis.
G.H.	58	F	Mass for 2 years with recent enlargement, dysphagia. PX--Mass in rt. thyroid region. BMR normal.	Solitary adenoma.	Subtotal lobectomy.	Predominantly trabeculated with sm.areas of sm. follicle formation. Capsule intact. No vascular invasion.	L & W 45 months after diagnosis.

SUMMARY OF SEVEN OUT-PATIENTS

THE ORIGIN OF THE HURTHLE CELL

In order to gain a proper perspective of the controversy concerning the origin,nature and behavior of these tumors, it is necessary to review the earlier work which has been done.

In 1894, Hurthle (7) described large, oxyphilic "inter follicular cells" which were "rich in cytoplasm" in the thyroid gland of puppies. These cells were thought by Hurthle to be normal gland constituents. Apparently, as a result of a statement by Ewing (8) in 1928, the name, "Hurthle cell tumor," became attached to a tumor found in human thyroid which is comprised of distinctive eosinophilic cells. Hurthle himself, however, made reference to the earlier work of Baber (9) who in 1877 described large oxyphilic cells in the thyroids of various laboratory animals. Baber termed these cells "parenchymatous" and believed them to be able to move from their interfollicular positions into the ordinary follicle and aid in producing colloid.

Nine years later, in 1886, Horsley (10) found acid staining "embryonic cells" below the thyroid capsule which he stated werecompletely encapsulated and definitely outsid e of the thyroid gland rroper. Langendorff (11) in 1889 substantiated the findings of Baber.

It remained then until 1898 before reference is made to to the human gland in this regard. At this time Askanazy (12)

described cells similar to those noted above in human thyroids in material from cases of thyrotoxicosis. Getzowa (13) in 1907 observed similar cells and theorized that they had developed from embryonic "rests" of the ultimo-branchial body. Langhans (14) shortly thereafter described a "small alveolar, large celled struma" and was impressed by the resemblance of cells of this tumor to those composing the liver and adrenal glands. He felt that it was possible that Getzowa's theory of ultimo-branchial origin was correct, although he felt additional confirmatory study was necessary.

Wegelin (15) has since cast a great deal of skepticism on this theory of origin, stating that too little proof is available to substantiate such a claim. Instead he postulated that Hurthle cells represented nothing more than functional variants of ordinary thyroid epithelium. To help illustrate his theory, he demonstrated a large cell adenoma which existed in the center of an ordinary type of thyroid carcinoma. In the zones surrounding the adenoma were cells which he felt represented all stages of intermediate cells.

Additional description of the "interfollicular cells" of Hurthle (7) has been made by Nonidez (16) in work on laboratory animals. He considered the parenchymatous cells of Baber (8) and the interfollicular cells of Hurthle identical with cells observed by him, which he gave a somewhat different name of "parafollicular". These cells he believed became transformed and separated from normal thyroid epithelium.

Zechel (17) also described parafollicular cells in laboratory animals and stated that he felt they probably represented a phase in the arrangement of thyroid parenchyma. Such a phase was thought to result from cystic degeneration and restitution of the ordinary follicle.

The existence of this cell in the human gland, variously termed interfollicular of parafollicular, has been seriously questioned, however. Lennox (18) states that although these cells may well exist in laboratory animals, adequate proof that they are present in human thyroid has never been shown. In addition, even in the animals in which they have been demonstrated, their presence is a transient thing, seen only in the first few months of life. Hurthle cell tumors on the other hand are, with rare exceptions, a condition prominent at the opposite endfof the life span. The relationship of the cells in this latter tumor are therefore felt to be quite remote from the interfollicular cells of these laboratory animals. Maximow and Bloom (19),by means of wax reconstructions, studied the thyroid and were unable to detect any evidence of interfollicular cells. It is their opinion that these cells actually represent, in some instances at least, tangentiallycut adjacent follicle walls which have been misinterpreted as distinct cells in the interfollicular areas. Williamson and Pearse (20) agree with Maximow and Bloom. In addition Marine (21) has found no evidence of histology in the human gland similar to that described by Hurthle, Baber, et al.

Although the ultimo-branchial origin of these cells has met with little confirmatory evidence, another essentially extrathyroid theory of origin has been advanced. Eisenberg and Wallerstein (22), particularly, conclude after extensive review of the subject, that "Hurthle cells" are identical with the oxyphile cells of the parathyroid gland. These authors believe that parathyroid "rests" within the thyroid occur, giving rise to tumorous growths under undetermined conditions. In order to emphasize this relationship, they cite cases in which clinical signs of hyperirritability are associated with "Hurthle cell" tumors. No confirmatory laboratory evidence was available, however these authors felt that the symptomatology suggested hyperparathyroidism. Sinclair and Larsen (23) in 1953 supported this theory by citing a case of intrathoracic Hurthle cell tumor which they state was composed mainly ofcells identical with oxyphile cells of the parathyroid. In addition other cells were represented which closely resembled chief cells of the parathyroid. No clinical or laboratory evidence of hyperparathyroidism was present in their data.

Most authors, as pointed out by Wilensky and Kaufman (24), feel that the theory of parathyroid origin is not warranted. These authors suggest that the symptoms of irritability and convulsive tendencies cited by Eisenberg and Wallerstein are not sufficient as evidence of hyperparathyroidism. Morrow (6) points out that these symptoms more nearly represent hypoparathyroidism.

An interesting new viewpoint regarding the nature of the Hurthle cells has recently been stated by Hamperl (25). By means of special staining technic, called "inclusion staining," Hamperl asserts that certain of the so-called Hurthle cells could be differentiated from others. He termed those cells which took up his stain, "oncocytes." This "oncocytic change," as he described it, has been demonstrated in the epithelium of other organs.including the salivary glands. In commenting on the studies of Hamperl, Lennox (18) states that the significance of the "oncocyte" is obscure, failing to clarify the already confusing picture of Hurthle cell change. This latter view seems at first glance to be natural, although the value of any evidence which may help to lend specificity to these controversial cells can not be underestimated. Judgment as to whether or not Hamperl's work represents such evidence must be withheld until further investigation is made.

In 1948 Willis (26) summarized the complexity of Hurthle cell argument. He states that all in all "Hurthle cell tumor" was an unfortunate name because: In the first place, there is no real evidence that the cells described by Hurthle are related in any way to the tumors bearing his name. Secondly, the very existence of interfollicular cells is in doubt. Thirdly, the particular eponymic name is unfortunate insofar as Baber described the same cells 17 years earlier.

The vast majority of authors, particularly within recent years, feel that extra-thyroid theories of origin are unjustified, and that beyond doubt whatever else may be their significance these peculiar cells are derived from ordinary thyroid follicular epithelium. This unanimity of opinion however leaves ample ground for argument because the reasons for this deviation from normal epithelium, as represented by Hurthle cells, is controversial, and the significance of the change once it has occurred is still mystifying.

Wegelin (15) regarded the eosinophilic cytoplasm and the vesicular nuclei of Hurthle cells as simple evidence of degeneration, comparable to that seen in anemic infarct of the kidney. Marine (21) felt that, rather than degeneration, the Hurthle cells represented epithelial cells in a particular stage of the secretory cycle of the thyroid gland. Maximow and Bloom (19) thought they were dead or dying cells.

Wilensky and Kaufman (24) have been particular proponents of the idea that Hurthle cells should not be regarded as anatomical entities. They observed these cells in benign thyroid conditions as well as in thyroid neo plasms, a point which they emphasize as of great importance. Their conclusions signify that patho-physiologic changes occur in thyroid epithelium, probably as a result of undetermined nutritional changes at a local level, the result of which is seen as the

"Hurthle cell change." Morrow (6) agrees that this theory best explains the presence of the cells in adults, although the rare case in infants more likely is a result of overgrowth of embryonal cells.

Childs (27) reviewed material from several cases of Hurthle cell tumor in 1951, and reported that his observations tend to show that Hurthle cells originate from two sources, ordinary follicular epithelium and nodules of young epithelium of the fetal cell type. In several cases he was able to show what appeared to be "a gradation of cell type" with apparently normal thyroid peripherally and Hurthle cells centrally. This change was seen as one passed in toward the degenerated center of the nodule, and, Childs felt, was extremely suggestive of a secondary change, probably on the basis of defective nutrition of the proliferating cells. He cites Lennox as designating this change a "metaplasia" and notes that Rawson (28) felt these cells were non-functional. Other studies on the functional aspect of Hurthle cells are noted below.

Friedman (29) took note of the fact that the predominant portion of work done in describing Hurthle cells largely had been a matter of studying material from tumors of the thyroid. This, as Friedman well illustrates, is misleading for these cells are frequently seen in conditions which are not regarded as neoplastic. The conditions in which he

observed Hurthle cells were myxedema, exhaustion atrophy, Hashimoto's disease, and reaction to irradiation, thiouracil therapy, and subtotal resection. Friedman emphasized that diffuse toxic goiter was frequently a preceding condition, and it is well known that the ultimate result of this condition is sometimes one of relative hypothyroidism clinically. The incidence of Hurthle cells was noted to be highest in hyperplastic glands, whose hyperplasia was aggravated by thiouracil treatment. In all cases, however, he postulated that thyroid cells were subjected to prolonged stimulation for one reason or another. This thought led Friedman to the conception that Hurthle cells, in part, illustrated a "cellular involution," which resulted from prolonged hyperplasia under stimulation; i.e., situations in which normal follicular involution was prevented from occurring by reason of the abnormal stimulation.

Whether or not Hurthle cells produce thyroxin has not been definitely proved. Most observers, such as Lennox (18), Sheiman and Kravchick (30), and Rawson (28), feel they are non-functional. Fitzgerald, et al., (31) studied the concentration of I^{131} in Hurthle cell tumors. Their series included nine cases, seven of which had a total of 13 primary lesions, and two of which had a total of 6 metastatic foci. Of the 19 separate lesions, only three foci, one of which was metastatic, showed concentration of I^{131}. Each foci was in a separate patient. Microscopic study of these concentrating

lesions revealed alveolar arrangement of the Hurthle cells, and a minute amount of colloid material was demonstrable within the alveoli. This same type of alveolar arrangement, including colloid formation, was demonstrable in other lesions which did not concentrate the radioactive iodine. These observations tend to prove that at least a small percentage of Hurthle cells retain the ability, however poorly, to concentrate iodine, and thereby produce thyroxine. Apparently microscopic differentiation of these functioning and non-functioning cells is not possible.

HURTHLE CELL TUMORS AND MALIGNANCY

No matter what theory of origin of the cell is favored, it should be emphasized that the Hurthle cell in itself is not to be regarded as a neoplastic cell. Neoplasms consisting predominantly of Hurthle cells of course are well established historically. The nature of these tumors is again controversial, and even their right to be designated a specific entity has been questioned by Pemberton and Black (32). However, the majority of authors consider it as distinctive by virtue of omission, for little mention is made to the contrary, nearly all emphasis being placed on the discussion as to whether the tumor is benign or malignant.

Stewart (33) feels that the tumors are specific anatomical entities and not merely a morphologic characteristic assumed by cells in various types of lesions.

Wilensky and Kaufman (24) have championed the opposite viewpoint. As noted before, they feel the Hurthle cell is a "patho-physiologic variant", probably on a nutritional basis, which may occur as easily within the structure of a tumor as under non-neoplastic conditions. This change may be extensive enough to involve the entire neoplasm. These authors emphasize the lack of success in the past in attempting to detect their benign or malignant nature on the basis of microscopic characteristics of individual cells or apparent cell behavior, such as blood vessel invasion. If, therefore, these men reason, Hurthle cells may develop incidentally in tumors as well as other conditions, perhaps one must seek identity of the original tumor cell type if malignancy is to be established. In addition, because Hurthle cells, according to these men, are essentially degenerative in nature, growth of the tumor may be slowed, particularly if an extensive Hurthle cell change has occurred. This, they conclude, may account for what appears to be a benign course in an essentially malignant tumor.

Lennox (18) lends support to the views of Wilensky and Kaufman, in emphasizing the importance of an antecedent cell type, rather than Hurthle cells themselves. He states that the Hurthle cell change occurs in two ways. The first he regards as a cell change in a fetal adenoma. This latter tumor, he asserts, is known to give rise to many types of carcinoma

of the thyroid. In some cases, then, the so-called Hurthle cell tumor may be seen. These latter tumors have a fairly uniform histologic pattern, are not associated with thyrotoxicosis, and are malignant in course. Lennox feels that this type of "Hurthle cell tumor" resembles the small alveolar, large cell tumor described originally by Langhans(14). The second type of tumor usually is associated with thyrotoxic adenoma, which has undergone Hurthle cell change (or "Askanazy cell change" as Lennox prefers to call it). This type is more common in females and histologically shows considerable lymphocytic infiltration. The course in the second type is usually benign. Exceptions to these two types, he feels, are seen in the Hurthle cell tumors of infancy, as described by Morrow (6) and Symmers (34), and probably are accountable on the basis of an embryonic overgrowth of fetal type cells. The matter of lymphocyte infiltration, it will be recalled, was also considered significant by Friedman (29). He found this phenomenon commonly associated with Hurthle cell change in benign conditions, such as myxedema, and therefore believed it to have benign connotation.

Bakay (35), though he differs from Wilensky and Kaufman (24) in regard to the origin of Hurthle cells, perhaps agrees essentially that degenerative changes may occur in this eosinophilic cell tumor, asserting that such a goiter corresponds to the type described by these two latter authors.

However he feels that this tumor is not the same as the one described by Langhans, a view somewhat similar to that of Lennox. It should be noted again that Hamperl has asserted that the Langhans type tumor has incorrectly been designated Hurthle cell tumor. His claim that this represents an adenoma or carcinoma undergoing "oncocytic change" has yet to be evaluated by a sufficient number of investigators.

While there remains much to be learned concerning the nature of these tumors, few recent workers would agree with Wegelin (15) who concluded in 1928 that these growths were simple adenomas. Sheiman and Kravchick (30) perhaps lean as much toward the overall benign side of the argument as any of the later investigators. They observed these tumors in association with normal thyroid epithelium, hyperplastic tissue, thyroid carcinoma, and as a tumor of uniform Hurthle cell structure. In general they believe that these tumors are slow growing, and do not metastasize; but even they conclude that the tumor should be regarded as potentially malignant if not overtly so.

Other authors hold a somewhat middle of the road opinion. Neidhardt (36) cites Reiman (37) as concluding that both benign and malignant forms exist. Symmers (34) held a similar view, as did Warren and Meissner (38) who classified Hurthle cell tumors as adenomas or adenocarcinomas in 1953. Foote, as cited by Chesky, et al. (2), believed that benign forms

could be detected by noting a uniform, orderly microscopic structure of tumor, whereas the malignant variety was disorderly in arrangement. Sedgwick (4) believed that preoperative diagnosis was impossible in regard to malignancy of this tumor. Goldenberg (1 agrees that such an attempt is difficult, but suggests the possibility of help from frozen section.

Harry (39) represents a school who believe that all Hurthle cell tumors are of moderate malignancy and should actually be regarded as adenocarcinoma. This school of thought appears to be dominant at present. Morrow (6) states that this tumor represents malignant or potentially malignant neoplasm. Frazell and Duffy also believed that Hurthle cell tumors were of moderate malignancy and easily demonstrated an ability to metastasize (5). The American Cancer Society has concluded in 1951 that Hurthle cell tumor should be classified as carcinoma or adenocarcinoma(40).

TREATMENT.

Because of the differences of opinion on the nature and significance of Hurthle cells, the recommended treatment for these tumors, once diagnosis is obtained, varies widely. Surgery in one from or another is almost universally regarded as the procedure of choice. The extent of resection necessary for adequate therapy shows no such uniformity of opinion, but naturally varies according to the

surgeon's or pathologist's belief regarding malignancy of the tumor.

Simple resection of the tumor mass itself was considered sufficient by Wegelin (15). Wilensky and Kaufman (24) replied that mere enucleation of the mass was not sufficient but required at least simple lobectomy.

Harry (39) believed that the tumors were of greater malignancy than could be coped with by lobectomy. He felt that bilateral thyroid resection with radical neck dissection was required in all cases. Sedgewick (4) more recently is inclined to agree.

These then constitute the range of recommended surgery. Most authors at the present time at least occupy positions somewhere in between.

Chesky, et al.(2), felt that in most cases lobectomy was sufficient. If regional nodes were palpable, or other clinical manifestations of local spread were noted, a more radical resection was in order. Goldenberg (1) expressed similar views in 1953.

Frazell and Foote (41) decided these tumors were of fairly high grade malignancy and that therapy must be adjusted accordingly. Later, Frazell, in conjunction with Duffy (5), recommended that if the tumor was clinically confined to a single lobe a complete lobectomy would usually suffice. They emphasize that lobectomy must be complete to be adequate;

for in their series of forty cases, seventeen patients had previously been operated (usually a partial lobectomy), and eight of these seventeen later died of their disease. In all cases of residual or recurrent tumor, they advise radical neck dissection.

The value of radiation therapy alone is generally felt to be inadequate to control the disease as noted by Frazell and Duffy, Goldenberg. Postoperatively, however, many, including Sedgwick (4), Wilensky and Kaufman (24), and Sheiman and Kravchick (30), feel that roentgen ray treatment may be helpful. Frazell and Duffy also concede that in unresectable or metastatic lesions, X-ray may be of palliative value. Irradiation by means of radioactive iodine, in most cases has little value, according to Goldenberg. He emphasizes the work of Fitzgerald, et al. (31), as noted above, who were able to demonstrate I^{131} concentration in only three of nineteen Hurthle cell lesions. Black, et al. (42), conducted studies to determine whether or not inoperable carcinoma of the thyroid could be selected for treatment with I^{131} on the basis of histologic features and type of lesion. Their conclusions were that Hurthle cell tumors were in a group which would not concentrate the radioactive substance initially. There was a slight possibility that administration of substances like propylthiouracil might stimulate the tumor to pick up the I^{131} subsequently.

PROGNOSIS

Most authors seem to agree with Morrow (6) who states that, whether or not Hurthle cell tumors represent cardinoma, the clinical course in the majority of cases is a fairly long one. Sheiman and Kravchick (30) go somewhat further by stating that these tumors are slow growing and generally do not metastasize.

The attempt of ascertaining relative malignancy of these tumors by notation of such histologic characters as bizarre variation in size and shape, number of mitoses, evidence of capsular erosion, or blood vessel invasion have been something short of satisfactory. Foote, as cited by Chesky et al. (2), has been one of the foremost to emphasize the possible significance of atypical cells in differentiating "benign" from malignant varieties. In his classification he divides Hurthle cell tumors into orderly and disorderly types, the latter of which offer a poorer prognosis especially when in conjunction with vascular invasion by tumor cells. Schenken(43) considers all Hurthle cell tumors carcinoma, and grades the tumors in individual cases according to relative degree of cell atypism. He has found poor correlation between vascular invasion and the degree of malignancy exhibited clinically.

Most authors tend to agree that such a view is correct. Goldenberg noted vessel invasion in eight cases, but only one of these showed subsequent metastasis. Chesky, et al.,

were unable to arrive at any significant correlation of the microscopic and clinical evidence of malignancy. Frazell and Duffy state that all of their patients with osseous metastasis show evidence of vein invasion. However, their conclusion is that vein invasion,per se, which at times is even grossly apparent, is no dependable prognostic guide.

These latter authors, it might be noted, regard this tumor as possessing greater malignancy than many other workers. In their series of forty cases, twelve died of their disease; two were post-operative deaths; four were living with the disease at the time of their review; four died of other causes with no evidence of disease; and eighteen were living with no evidence of disease. Their series included seventeen patients previously treated for Hurthle cell tumor, and it is their opinion that the most important single prognostic guide is the stage of the disease on admission.

Sedgwick (4) is inclined to agree with them, stating that the prognosis is poor in adenocarcinoma of the thyroid with Hurthle cells in cases in which metastasis has already occurred. He reviewed five of such cases, four of whom were dead in three months, and fifth died within nineteen months. He notes that cases treated by thyroidectomy before evidence of metastasis was demonstrable offered better prognosis.

Frazell and Foote (41) conclude that, although the course of Hurthle cell cancer is apt to be prolonged, the

opinion that these tumors are of low-grade malignancy was not borne out by their studies. The average duration of life, from the time of diagnosis to the time of death, was 59.7 months, and that only one-third of their series were alive after five years.

The five year survival rate, free of signs of disease, in the small series covered in this review was seen to be only 8%: however 53% of the patients are living and well for periods ranging from eight months to almost four years. Attesting also to the prolonged course of this type of tumor was the fact that two patients who ultimately developed metastatic lesions to bone survived for periods of 11-1/2 and 9 years, respectively, following initial surgery.

In the series of twenty-five cases reported by Chesky, et al. (2), a five year survival rate in patients free of disease was 20%. An additional 12% had survived well over five years although evidence of recurrence was present. At the time his review was made, the overall number of patients living and well was 88%.

Goldenberg (1) shows a 41 % five year cure rate in his series of 22 patients. An additional 27% were living and well less than five years postoperatively. A total of 90% had survived six years in spite of evidence of existing disease.

SUMMARY

Thirteen new cases of Hurthle cell tumor have been presented, and statistical data obtained from these cases are compared with figures obtained from the literature. Uniformly

more frequent in females than in males, these tumors are generally said to constitute 3 to 10% of all thyroid malignancies, and are much more common after age 40. Patients developing these tumors present wide variations in history and physical findings, although generally the history reveals the presence of a mass for several years and physical examination suggests a solitary adenoma. Histologically, the tumors are all composed of typical eosinophilic Hurthle cells, but considerable variation in cellular arrangement is seen: trabecular, alveolar, large follicle, papillary and mixed. In some reviews, there is stated to be possible histologic and clinical correlation of malignancy, particularly regarding the demonstration of capsular erosion and vascular invasion. In this series, however, and in the majority of other studies, no good correlation was found. Even those people who so emphasize the importance of such behavior admit that it is not a good prognostic guide.

The theories of the origin and nature of Hurthle cells has been reviewed. Those theories regarding interfollicular cell, parafollicular cell, ultimo-branchial, or parathyroid origin have all been quite generally unsupported. Hamperl's introduction of the theory of "oncocytic change" has yet to prove its significanceand requires further investigation. Until this can be done, it will generally be accepted that Hurthle cells are not in themselves anatomic entities, but

are functional or degenerative variants of ordinary or neoplastic thyroid epithelium. This theory best explains the prolonged and apparently benign course taken by the tumor which in many other ways fulfills criteria for malignancy. It seems important that if an original cell type can be demonstrated it would have greater prognostic value.

Treatment varies widely but in most cases of tumor confined to a single lobe, complete or subtotal lobectomy is considered adequate. The place of total thyroidectomy and radical neck dissection seem at present to be limited primarily to cases of recurrent tumor or tumor with regional node metastasis. Irradiation, externally or by means of I^{131}, has minor and palliative value.

The course of this disease is generally prolonged compared to many neoplastic conditions. Although the five year cure rate ranges from 20 to 40%, many examples of survival of over five years are seen in patients with proven recurrence or distant metastasis. Prognostically, the most valuable guide is the stage of the disease when first seen.

CONCLUSIONS

1. Thirteen new cases of Hurthle cell tumor have been presented and statistical comparison made with other studies.
2. Origin of Hurthle cells is probably from ordinary or neoplastic thyroid epithelium, and represents a basically degenerative change.

3. Malignancy of these tumors, in view of their probable origin, depends primarily upon the antecedent cell type. Ordinary means of determining malignancy histologically correlates rather poorly with the clinical course.
4. Recommended treatment is complete or subtotal for cases with lesions confined to a single lobe. Complete thyroidectomy and radical neck dissection are necessary in cases of recurrent tumor or tumor metastatic to regional nodes.
5. The course of this disease is usually prolonged, depending upon the stage in which the disease is first seen. A 20 to 40% five year cure is reported in most studies. Survival in the presence of disease often extends beyond this point.

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