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The Dependency of Thyroid Cancer

A Review *

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Biologic Considerations

THE BIOLOGIC characteristics of certain types of malignant neoplasms have suggested that autonomy of growth may be a quantitative rather than a qualitative phenomenon. In these neoplasms, it is probable that similar factors influence both normal and neoplastic cellular growth. Whereas in most organ systems, the factors governing cellular metabolism are relatively obscure, the endocrine system is unique in that the trophic hormones are well known. Not only do these hormones regulate normal cellular growth and function, but they also may influence neoplastic growth arising in target organs. While carcinoma of the breast and carcinoma of the prostate are well recognized examples, there are apparently other tumors of the endocrine system which may exhibit a similar relationship to their trophic hormone, namely, adrenal carcinoma to ACTH,[20] thyroid carcinoma to TSH,[49] and uterine tumors to estrogen.[40] These neoplasms have been termed "dependent" or "conditioned" since their growth may be enhanced or modified by their hormonal environment. That a hormonal stimulus can serve as a factor in the development of a malignant tumor was first noted in mammary tumors in rats. Breast adenomas transplanted into a pregnant rat grew at an extraordinary rate but at the conclusion of pregnancy, retrogressive changes developed in the tumor as well as in the normal mammary tissue.[28] "Conditional growth" has also been observed in other experimental tumors such as the "tar warts" of rabbits where without continuous stimulation regression was noted to occur.[45] This reversibility of growth may be more common than is realized in human tumors since the concept of "irreversibility" is based upon observation of successful neoplastic growth which may represent transition from dependency to increasing autonomy. This transition has been noted repeatedly in endocrine tumors in man. Similarly, in the experimental animal following appropriate hormonal stimuli, transition from normal to

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hyperplastic to conditioned and finally autonomous growth may occur.[22] This change in the direction of autonomy is apparently a gradual one and only in part a function of time. Since hormones are probably in some way connected with activities of enzymes, it may be that the ability of cells to grow in the absence of their hormonal stimulus represents an adaptive mechanism (mutation, substitution, or deletion of genes) enabling such a cell to survive and grow despite the lack of this particular enzyme system.[13] This adaptation may be somewhat comparable to the bacterium in its development of drug-resistance.

Whereas the implications of such concepts in the management of malignant disease such as carcinoma of the prostate and carcinoma of the breast have been widely accepted and utilized,[26] relatively little attention has been directed to the application of this concept in the management of other neoplasms of the endocrine system. The purpose of this review is to focus attention upon the apparent dependency of certain thyroid neoplasms upon thyrotropic stimulating hormone. Not only can growth and function of thyroid cancer be enhanced, but conversely inhibition or regression of thyroid cancer may occur following appropriate alteration of its hormonal environment.

Observations upon experimental animals as well as upon man have attested to the dependency of thyroid neoplasms upon thyrotropic hormone. Experimental thyroid tumors, benign and malignant, dependent and autonomous, have been produced in both the mouse and rat. In the genesis of these tumors, either a carcinogen or the hereditary factor of a high tumor strain apparently can serve as an initiating factor, whereas a goitrogen, which acts by reducing circulating thyroxin, increases thyrotropic hormone and serves as the promoting factor.[25] The administration of propylthiouracil to a strain of mice with a low incidence of tumors is followed by hyperplastic nodules and so-called benign tumors of the thyroid. If a high tumor strain of mice is employed, malignant and autonomous tumors develop.[21, 33] In the rat, administration of a goitrogen alone (antithyroid drugs or iodine deficiency) may produce benign as well as malignant tumors.[1, 32] Although cancer of the thyroid may be produced in rats by such means, the concomitant administration of a carcinogen such as acetylaminofluorene appears to shorten the latent interval required.[14] The greatest incidence of formation of tumors occurs in those animals receiving a carcinogen, a goitrogen and radioactive iodine. Most of these tumors remain dependent but a few attain complete autonomy with ability to metastasize and grow in the absence of elevated levels of thyrotropic hormone. Since in some instances the carcinomas produced appear to be under the influence of thyrotropic hormone, as long ago as 1947, Purves and Griesbach stated: "It may therefore be possible to influence the course of malignant thyroid disease in human beings by the therapeutic administration of desiccated thyroid."[39] In keeping with this concept, spontaneously occurring thyroid tumors in the xiphophorin fishes have been observed to regress following the administration of potassium iodide, thyroxin and mammalian thyroid tablets.[5]

There is some evidence that in man a situation exists similar to that in the experimental animal. In many instances, the development of thyroid cancer in children has been preceded by the administration of high voltage roentgen therapy.[9, 15, 47] The carcinogenic effects of x-rays are well known and this would seem to simulate very closely the role of initiating factors in the experimental animal. Another counterpart of these experiments is occasionally seen in goitrous cretins[27] and in a few patients with a non-toxic hyperplastic nodular goiter.[4] In these individuals, there is apparently an intrinsic defect in the syn-

thesis of thyroid hormone resulting in compensatory hyperplasia produced by thyrotropic hormone in response to a low circulating thyroid hormone level. Such goiters exhibit a varied histologic appearance including diffuse epithelial hyperplasia, small follicles and embryonal and colloid adenomas. Invasive cancer has been demonstrated in three such individuals [38, 44] and the histologic appearance in others is suggestive.

Further support of the relationship of neoplasia to thyrotropic hormone is obtained from the incidence of cancer in nodular goiter. The development of a nodular goiter implies the presence of some type of goitrogen and adequate stimulation by thyrotropic hormone. Perhaps the best evidence of a significant relationship comes from Switzerland where when iodine deficiency was common, deaths from thyroid cancer were ten times that in non-endemic areas. Following correction of iodine deficiency, deaths per hundred thousand decreased by two-thirds.[57] It is difficult to reconcile this observation with the fact that the incidence of nodular goiter increases with age [42] whereas that of thyroid cancer reaches its peak about the fifth to sixth decade.[36] Furthermore, in hyperthyroidism, the incidence of thyroid cancer is distinctly lower in the toxic nodular goiter (1 per cent) and in diffuse toxic goiter (0.1 per cent) than it is in non-toxic nodular goiters (4.5 per cent).[3]

Examination of the biologic characteristics of human thyroid cancer reveals that in the more common varieties of this neoplasm, namely papillary and alveolar cancer, the same trophic stimuli may regulate neoplastic as well as normal thyroid activity. It is not unusual for tumors of the thyroid to arise at a much earlier age than most malignant neoplasms, being relatively common in the second and third decades of life.[55] This is at a time when the physiologic demands upon the thyroid are high. If a physiologic stimulus can serve as a promoting factor, there should be multiple foci of origin of these tumors, and this seems to be borne out in carefully studied cases.[30] Further support of the role of a physiologic stimulus comes from a study of the anterior pituitary gland in such patients. There has been noted an increase in the amophil cells which serve as the primary source of thyrotropic hormone.[46]

Most tumors that arise in childhood seem somewhat considerate of the host since although they may metastasize to lymph nodes and lungs, they grow slowly and in many instances seem to have little ill effect. The natural history of thyroid tumors indicates that they may become increasingly aggressive since, in general, the greater the duration of the disease the more malignant the neoplasm despite the lack of any change in its morphologic characteristics.[48] As a corollary, the older the patient in which thyroid cancer develops, the more likely is the tumor to be an aggressive neoplasm without the vagaries of behavior cited above.[12] This increasing malignancy with age is somewhat comparable to the experimentally induced neoplasms of the thyroid which though initially dependent may finally become autonomous.

Both function and growth can be demonstrated to respond directly to hormonal stimuli. Many years ago Von Eiselberg [52] demonstrated that metastatic thyroid cancer in the absence of the normal thyroid was capable of sustaining normal metabolic function. This observation has been confirmed on many occasions since that time. In addition, an increased growth of thyroid cancer has been noticed incident to "preparation" of the patient for treatment with radioactive iodine.[29] This "preparation" involves increasing the level of thyrotropic hormone either by way of the anterior pituitary or by direct administration. During such a period of stimulation, metastases have been observed to increase in size as well as destructive properties. The converse has also been noted in that a patient

TABLE 1. *The Effect of Exogenous Thyroid Hormone on Thyroid Cancer*

Author	Year	Age of Patient	Sex	Type of Carcinoma	Duration of Disease	Extent of Disease	Previous Treatment	Treatment with Desiccated Thyroid	Duration of Treatment	Other Treatment	Results
Bruns[8]	1896	No. of patients and type of carcinoma unknown.						3 Gr. fresh thyroid			"Totally inaccessible to thyroid treatment."
Dunhill[16,17]	1937	8	F	Well differentiated adenocarcinoma	5 yrs.	Confined to neck without lymph node metastases	Surgery twice, x-ray	"Large doses"	Continuous until present (1956)		Mass completed disappeared.
		24	F	Well differentiated adenocarcinoma	19 yrs.	Confined to neck without lymph node metastases	Surgery twice, radium	"Large doses"	Continuous until present (1956)		Mass resolved completed.
	1956	child	F	Papillary adenocarcinoma	1 yr.	Neck, lymph nodes with pulmonary metastases	Partial thyroidectomy and lymphadenectomy	"Unknown but recently 1 Gr. daily"	17 yrs.		All metastases have disappeared from lungs by x-ray.
Balme[2]	1954	40	F	Well differentiated adenocarcinoma	8 yrs.	Pulmonary metastases	Surgery, x-ray	Thyroxin, .5 mgm.	2 yrs.		Reduction of dyspnea with slight but definite clearing of pulmonary metastases.
Ward[52]	1955	16	?	Papillary adenocarcinoma	12 yrs.	Confined to neck with lymph node metastases	X-ray	Tolerance doses	12 yrs.		Disappearance of tumor in neck and thyroid for 10 yrs., with recurrence after cessation of thyroid treatment. Maintained on 2 Gr. of thyroid after total thyroidectomy and neck dissection. Small mass recurred 2 yrs. later.
Crile[12]	1955	5 patients		Papillary adenocarcinoma	Unknown	Pulmonary metastases	Unknown	3–4 Gr. daily	1–5 yrs.		"Cessation of growth in every case and in some complete disappearance of tumors in neck and chest."
		2 patients (age is unknown)		Papillary adenocarcinoma	Unknown	Bone		3–4 Gr. daily	1–5 yrs.	X-ray	"Arrest of growth with recalcification."
Trunnell[51]	1956	25 patients (age is unknown)		Dose of desiccated thyroid relatively small and designed to maintain euthyroid status.							No regression seen in any of patients.
Bierwaltes[6]	1956	"Boy"	M	Papillary adenocarcinoma	Unknown	Confined to thyroid	None	3 Gr. daily	3 mo.		No regression of nodule in three mo. At operation papillary adenocarcinoma which was unaltered morphologically.
		19	F	Adenocarcinoma	3 yrs.	Pulmonary metastases	Radioactive iodine (apparently ineffective)	Tolerance dose with average of 3 Gr. daily	3 yrs.		"Negative chest for 3 yrs. with masses disappearing from neck (possible late effect of radioactive iodine)."
Rawson[40]	1956	?	?	Unknown	Unknown	Bone metastases	Unknown	Large doses of triiodothyronine			No change in rate of calcium loss in urine.

TABLE 1—*Continued*

Author	Year	Age of Patient	Sex	Type of Carcinoma	Duration of Disease	Extent of Disease	Previous Treatment	Treatment with Desiccated Thyroid	Duration of Treatment	Other Treatment	Results
		?	F	Functioning by radioiodine studies	Unknown	Pulmonary metastases	25 Mc. of radioactive iodine	3-4 Gr. daily	Several mo.		Regression of pulmonary metastases (severe infection and previous radioiodine make evaluation of treatment impossible).
Maloof[29]	1956	60	F	Adenocarcinoma arising in embryonal adenoma	4 yrs.	Pelvic metastases	Radioactive iodine, x-ray	3 Gr. daily	18 mo.		No progress in growth of tumor. Needle biopsy showed small nests of tumor cells in fibrous tissue. Cells and acini appeared more atrophic than in previous biopsy.
		73	F	Follicular carcinoma	1 yr.	Rib metastases	Radioactive iodine	4 Gr. daily	18 mo.		Metastases remained stationary.
		25	F	Papillary adenocarcinoma	Unknown	Neck with axillary and pelvic metastases	X-ray, Testosterone		5 mo.		Death in 5 mo. No inhibitory effect on growth.
		32	F	Hurthle cell carcinoma	Unknown	Metastases to skull, lungs, clavicle and vertebrae	X-ray		6 yrs.		No inhibitory effect.
Craver[10]	1956	49	F	Small alveolar cell carcinoma (slight function by I^{131} studies in pulmonary metastases	28 yrs. (Partial thyroidectomy; bony metastases of 13 yrs.)	Metastases to left ilium, sacrum, 7th dorsal vertebra and left 10th rib with paraplegia	X-ray to bony metastases, 10 year remission. Radioiodine with no improvement. Clinical myxedema at this time	2 Gr. daily	6 yrs.	Physiotherapy	"Complete rehabilitation within one year. Recent x-rays show no change in multiple bone or lung metastases. The growth of this neoplasm may have been enhanced by the associated myxedema."
Moore[31]	1957	43	F	Alveolar and papillary carcinoma	6 yrs. Bony metastases 4 yrs.	Metastases to skull, humerus, thoracic spine ribs, pelvis and both femurs with paraplegia	Partial thyroidectomy, 5/51. Total thyroidectomy, 1955. Radioiodine, 1955. X-ray, 1955 (all without effect)	2 Gr. daily with increase to 6 after 2 weeks, 8 after 8 weeks. Because of nervousness and anorexia dosage reduced to 4 Gr. daily	1 yr.		10 mo.—gain of 18 lbs., regression of scalp metastases, partial reossification of metastases of skull, spine, pelvis and left femur. Return of urinary continence.
Thomas[49]	1956	29	F	Papillary and alveolar adenocarcinoma	7 yrs.	Multiple lymph node metastases	None	3 Gr. daily	3 wks.		Total thyroidectomy and right radical neck dissection performed at end If treatment period. No morphologic change in neoplasm was noted.
		36	M	Solid and alveolar	1 yr.	Massive cervical node and pulmonary metastases	None	5 Gr. daily	6 mo.	X-ray to neck	Initial regression of cervical metastases (x-ray effect?) but progression of pulmonary metastases. Later, progression of cervical metastases while on therapy with sudden death.

TABLE 1—*Continued*

Author	Year	Age of Patient	Sex	Type of Carcinoma	Duration of Disease	Extent of Disease	Previous Treatment	Treatment with Desiccated Thyroid	Duration of Treatment	Other Treatment	Results
		74	F	Alveolar and poorly differentiated adenocarcinoma	3 mo.	Invasion of strap muscles and trachea with cervical node and pulmonary metastases	Total thyroidectomy and modified neck dissection	3 Gr. daily	2 mo.	None	Rapid progression of disease with death in two months.
		60	F	Solid papillary and alveolar carcinoma	3 mo.	Pulmonary metastases	Total thyroidectomy	3 Gr. daily	1 mo.	one	Regression of metastases in right lung with rapid progression on left side and death at six weeks.
		50	M	Papillary adenocarcinoma	7 yrs.	Metastases to clavicle, ulna, vertebrae and lungs	Partial thyroidectomy and neck dissection	5 Gr. daily, later 200 mcg. triiodothyronine daily	4 mo. 3 mo.		Progression of all bony and pulmonary metastases with death 18 mo. after onset of therapy from complications of paraplegia.
		65	F	Papillary and alveolar	1 yr.	Confined to thyroid gland	Biopsy only	2 Gr. daily	30 mo.		Decrease in tumor by clinical evaluation. Biopsy at 15 mo. disclosed hyperplasia of normal thyroid with questionable increase in fibrous connective tissue around neoplasm.
		33	F	Papillary and alveolar	3 mo.	Bilateral cervical node metastases	Total thyroidectomy. Modified neck dissection	3 Gr. daily	30 mo.		No clinical evidence of progression although residual metastatic disease in neck by uptake of radioiodine.
		22	F	Papillary and alveolar	Undetermined	Confined to thyroid gland	2,000 R for hyperthyroidism at 6 yrs.	200–300 mcg. of triiodothyronine	6 wks.		Clinical evidence of regression at time of total thyroidectomy. No definite morphologic regression.
		31	F	Papillary and alveolar carcinoma	1 yr.	Lymph node and pulmonary metastases	None	5 Gr. daily	30 mo.	Total thyroidectomy after 1 yr.'s treatment	Clinical regression of primary tumor with regression of pulmonary metastases by roentgen examination.
		56	F	Papillary and alveolar carcinoma	7 yrs.	Pulmonary metastases	Partial thyroidectomy	3–5 Gr. daily, later 100–150 mcg. of triiodothyronine daily	36 mo.		Initial regression of pulmonary metastases. Late progression of cervical neoplasm as well as one pulmonary metastasis.

with metastatic thyroid cancer had decrease in the size of pulmonary metastases following the coincidental development of hyperthyroidism.[11]

The Effect of Pituitary Depression on Human Thyroid Cancer

These experimental and clinical considerations support the concept that cancer of the thyroid often at onset is not entirely an autonomous neoplasm and that alteration in the level of thyrotropic hormone may be reflected in the growth of the neoplasm. Since there exists a reciprocal relationship, elevation of the blood thyroid hormone is followed by inhibition of the pituitary gland and a fall in thyrotropic hormone.[37] Consequently, following the administration of desiccated thyroid, there is atrophy of the normal gland histologically [43] and loss of function as measured by the uptake of radioactive iodine. Evidence gleaned from suppression of the radioactive iodine uptake, elevation of the protein-bound iodine and requirements for treatment of simple goiter and myxedema suggests that from 2 to 4 Gr. of desiccated thyroid daily will suppress the endogenous output of thyrotropic hormone by the anterior pituitary.[22, 23]

Although there has been considerable experience in the administration of desiccated thyroid to normal individuals and in certain physiologically altered states, there has been limited experience in appraising its effect on thyroid cancer (See the Table). Thyroid hormone was used as an adjunct in the palliative treatment of many types of malignant disease in the early part of the 20th century, but only Bruns [8] cites any specific experience in the treatment of thyroid cancer. In discussing the results of the treatment of "parenchymatous" goiter he states: "Excluded only are the cases of cystic goiter and of malignant struma. These two are from the beginning totally inaccessible to thyroid therapy." He administered desiccated thyroid containing an equivalent of 0.3 Gr. of fresh thyroid gland daily but unfortunately gave no details as to the type of neoplasm treated.

In his Lettsomian lectures in 1937, Sir Thomas Dunhill [16] cited two children with recurrent carcinoma of the thyroid both of whom had been operated upon twice for recurrence and one of whom had received interstitial radium. In both patients, the thyroid mass disappeared with fairly large doses of thyroid. One child has since married, had children and it has been necessary to continue the dose of thyroid to prevent increase in the size of the gland. Although both of these tumors were reported as malignant, Dunhill commented: "There is much that we do not yet know about carcinoma of the thyroid and proliferation of thyroid epithelium, but I cannot help thinking that hyperplasia in response to demand or stimulation can closely approach the appearance which simulates malignancy." In 1939, Dunhill treated another child with "papilliferous adenocarcinoma" of the thyroid with cervical lymph node and diffuse pulmonary metastases. During the ensuing 17 years this patient has continued on thyroid, all deposits have disappeared from the lung, and the patient has married and has had several children.[17]

It was at Dunhill's suggestion, in 1942, that Ward [53] administered desiccated thyroid to "suppress the growth of thyroid cancer" in a child of four and one-half years. Following this therapy and in conjunction with high voltage roentgen-ray therapy, the tumor in the neck rapidly disappeared and remained so for approximately ten years. The exogenous thyroid was discontinued at this time and the tumor rapidly returned in the neck and thyroid gland. The histologic pattern was the same as it had been ten years previously. More recently Balme [2] cites a 40-year-old female with a highly differentiated tumor and widespread pulmonary metastases that responded favorably to the administration of L-Thyroxin. This patient had a mass in the neck of 21 years' duration and pro-

gressive pulmonary metastases for eight years. Following a total thyroidectomy, radioiodine studies disclosed a 30 per cent uptake in the chest and 9 per cent in the neck. However, there was no appreciable improvement following 122 millicuries of radioiodine. Nine months after the last therapeutic dose of radioiodine, l-thyroxin was administered in a dose of 0.1 mg. daily and slowly increased to 1.0 mg. and then reduced to 0.7 mg. with minimal toxic symptoms. On this dosage, there was excretion of 99 per cent of a tracer dose of radioiodine. After being maintained on 0.5 mg. of l-thyroxin daily with observation for six months, there was a slow but considerable reduction in dyspnea with a rise in maximal breathing capacity and a slight but definite clearing of the lung by x-ray examination.

Crile [11] has reported his experience in the treatment of five patients with pulmonary metastases of papillary carcinoma by the administration of desiccated thyroid. In observations varying from one to five years, in every instance there was cessation of growth of the carcinoma. In some there was complete disappearance of tumor both in the neck and chest. In two other cases with solitary metastases in bone, there was an arrest of cancer growth and recalcification during treatment with desiccated thyroid supplemented by roentgen-ray high voltage therapy. There were no favorable responses in patients with highly malignant or undifferentiated cancers of the thyroid. Recurrence of tumors of low malignancy treated with desiccated thyroid did not develop in patients who only had partial removal of extensive papillary carcinoma.

Bierwaltes [6] has observed the effect of thyroid administration on two patients with thyroid cancer. In one, a papillary adenocarcinoma of the thyroid was not altered morphologically by 3 Gr. of thyroid daily for three months. A second patient in whom there was prior treatment with radioactive iodine with an apparently poor response had complete regression of cervical and pulmonary metastases. This patient has had a normal chest film for approximately three years. Trunnell in a more extensive experience detected no regression in any of 25 patients.[51] The doses of thyroid employed, however, were small and designed only to maintain a euthyroid state. Maloof [29] has noted regression in patients with pulmonary metastases, whereas bony lesions have been kept stationary. The usual daily dosage employed was 3 to 5 Gr. of thyroid by mouth and more recently 75 to 100 mcg. of l-triiodothyronine sodium. Rawson [41] has tried to suppress the growth of thyroid cancer with thyroid hormones and cites two cases. In one with extensive bone metastases producing hypercalcuria and hypercalcemia, large doses of l-triiodothyronine did not reduce the rate of calcium loss in the urine. In the other patient 3 to 4 Gr. of desiccated thyroid daily was followed by some regression of bony metastases after a few months. Because of other factors, including a severe infection and 25 millicuries of radioactive iodine, he thought it was difficult to attribute regression entirely to the administration of thyroid hormone.

Moore [31] noted a dramatic remission of the growth of multiple bony metastases in a patient whose disease probably had been present for at least six years. Metastases had progressed to pathologic fracture and paraplegia. Although there was uptake of tracer quantities of radioiodine by neoplasm, there was no clinical improvement following therapeutic amounts. After the administration of 4 to 8 Gr. of desiccated thyroid daily there was evidence of reossification of the osteolytic bone lesions and recovery from the urinary incontinence. This patient showed evidence of response within three months after initiating treatment and has continued to show a beneficial response during the ensuing nine months.

A somewhat similar patient has been reported by Craver *et al.*[10] In 1927, at the age of 21, their patient had removal of a small cell alveolar carcinoma of the thyroid. Pain was noted in the left hip in 1936, and by 1940, x-ray examination disclosed osteolytic lesions in the wing of the left ilium, left sacrum and seventh dorsal vertebra which on biopsy disclosed metastatic thyroid carcinoma. X-ray therapy was followed by considerable relief of pain. Radioiodine studies, in 1946, disclosed normal uptake over the thyroid and none over the metastases. In 1950, a new lesion appeared in the left tenth rib and 50 millicuries of radioiodine were administered. X-rays of the other bony lesions disclosed no essential change. Following evidence of spinal cord compression, a laminectomy revealed metastatic thyroid cancer and gave temporary relief. In October 1950, with clinical evidence of myxedema, radioiodine tracer studies disclosed some pickup over metastatic disease in the lungs as well as low uptake over the neck. Following treatment with large doses of thiouracil without much effect, the patient was placed on 2 Gr. of thyroid daily and gradually began to improve. The thiouracil was discontinued and within the next year she made a complete rehabilitation. Recent x-rays disclosed no significant change in multiple bone or lung metastases.

Our experience during the past three years in the management of ten patients over varying periods of time by the administration of exogenous thyroid hormone has confirmed the dependent status of many of these tumors. Except for surgical excision no adjuvant treatment has been employed so that the effect of TSH suppression alone could be evaluated (see the Table). All but one of those patients with alveolar or papillary carcinoma exhibited regression or apparent inhibition of their tumors. In those in whom there was no response to decrease in thyrotropic principle, the neoplasm was for the most part either poorly differentiated, mixed in character with areas of poor differentiation or the small celled variety. The histologic pattern of the neoplasm is not alone always a good criterion of susceptibility, since one patient with a papillary and alveolar carcinoma (but without colloid production) that morphologically seemed identical to neoplasms showing a dependent response, failed to exhibit any gross retardation or inhibition of bony or pulmonary metastases despite 5 Gr. of thyroid daily for three months followed by 200 mcg. of triiodothyronine daily for two months.

Discussion

In attempting to determine the responsiveness of human thyroid neoplasms to changes in their hormonal environment, not only must the dependency of the individual tumor be evaluated, but there first must be adequate suppression of pituitary function. For the most part, it has been difficult to evaluate the efficacy of TSH suppression on thyroid cancer since inadequate amounts of exogenous thyroid hormone may have been administered and in addition, adjunctive therapeutic measures were frequently employed.

In the absence of being able to determine the thyrotropic hormone level directly, the adequacy of pituitary suppression can only be inferred from inhibition of thyroid function. The use of l-triiodothyronine as a pituitary depressant has several advantages over other thyroid hormones by virtue of the immediacy and duration of its action as well as its apparent lack of firm binding by serum proteins.[50] This latter biochemical characteristic permits a quantitative measurement of endogenous thyroid hormone while the patient is being maintained on l-triiodothyronine. With adequate dosage the serum protein-bound iodine falls progressively to hypothyroid ranges. That this level represents fairly complete suppression of thyrotropic hormone and thyroid inhibition is evident by the lack of any

further fall in the protein-bound iodine subsequent to total thyroidectomy. Although the uptake of radioiodine may be depressed and the output of endogenous thyroid hormone may fall to hypothyroid ranges, these are primarily measurements of function rather than growth. The possibility that growth and function of the thyroid gland may be controlled independently by way of the pituitary points out the need for determining whether thyrotropic hormone depression inhibits growth as well as it apparently inhibits function.[24] The incorporation of radiophosphorus into the thyroid cell may be of value in serving as a more precise method of measurement of growth.[7]

It is apparent that some types of thyroid neoplasm exhibit a very striking dependence upon thyrotropic hormone and that the progressive course of this disease may be altered by capitalizing upon the lack of tumor autonomy. Although all functioning tumors can probably be influenced favorably by hormonal therapy, the lack of function indicated by the absence of colloid production or iodine binding as evidenced by uptake of radioiodine is not necessarily a criterion of autonomy. This is particularly true when the tumor is competing with normal thyroid tissue, for under such circumstances it is difficult to show iodine uptake by radioautographic studies. Under maximal stimulation only the giant and spindle-cell carcinomas of the thyroid have been shown to be absolutely incapable of trapping iodine.[18] The relationship between function and growth has not been clearly defined and there is some evidence that they may be independently controlled. Certainly, it is highly possible that the growth of a neoplasm may be retarded or inhibited by TSH suppression even though function cannot be demonstrated. Papillary and alveolar cancers which are the most common histologic types are fortunately also the most sensitive to their hormonal milieu. In all likelihood those neoplasms which are completely independent of thyrotropic hormone will probably be found to possess no affinity for iodine. This has already been nicely demonstrated in spontaneous thyroid tumors occurring in animals.[56]

From the available data, there is no apparent difference in the response between primary neoplasm and its metastases. Perhaps, because of their ease of identification, pulmonary metastases seem to regress more readily following TSH suppression than do metastases to bone or lymph nodes. However, tumors of the same histologic pattern may show varying degrees of dependence. This difference in function cannot be noted with ordinary staining technics.

The neoplasms exhibiting the most dramatic response have been those present for long periods of time. This is an excellent example of Weiss' concept of self-regulating effect of the growth of tissue by its own products.[54] Usually, these patients have shown little systemic evidence of malignant disease unless the neoplasm by virtue of its location, size and local destructive properties has caused a deterioration of the host's general condition. Consequently, pulmonary metastases give no symptoms until interference in ventilatory capacity is noted, and similarly, bone metastases unless accompanied by pain, pathologic fracture or neurologic deficits are seldom associated with any systemic reaction.

Although reduction in size of the neoplasm has been observed grossly and radiologically, there have not been a sufficient number of histologic studies following prolonged pituitary suppression to enable one to demonstrate any well-defined effect on the neoplasm. Time may be a most important factor since even with loss of growth and functional stimuli, there may be residual activity within the gland and morphologic changes appear slowly. The neoplastic cells, however, do not appear as atrophic as do the cells of the nearby "normal" acini. The lack of colloid production seems to be a feature in common. A rela-

tive increase in fibrous stroma about the neoplastic cells has also been observed and is similar to that seen in carcinoma of the breast and prostate following treatment by endocrine methods.

Just as in experimentally produced thyroid neoplasms and in human breast and prostatic cancer, dependency appears to be a quantitative phenomenon, for with time greater autonomy of growth develops. This may or may not be associated with morphologic change in the neoplasm and does not affect all of the cells in a single neoplasm identically. Many times the development of autonomy is progressive, suggesting a mosaic effect.

Since the predominant neoplasm of the thyroid is papillary or alveolar carcinoma, this approach has implications in prophylaxis as well as therapy. Its role in treatment needs further study to determine criteria of susceptibility as well as optimum dosage of exogenous thyroid hormone. As a means of prophylaxis this concept has perhaps ever greater implications if thyrotropic hormone is a factor in the development of thyroid cancer. The high incidence of "occult" thyroid cancer is just becoming apparent,[35] and a partial thyroidectomy in such a patient or other goitrogenic stimulus may result in a relative preponderance of TSH and conceivably an increasingly autonomous neoplasm. By adequate pituitary suppression in these individuals, the development of thyroid cancer may be as effectively decreased as it apparently was in Switzerland following the introduction of iodine.

The need for total thyroidectomy in treatment of cancer of the thyroid should also be apparent, for only by this means can all potential or multi-focal thyroid cancer be excluded from subsequent growth stimulus. However, once having performed a total thyroidectomy it is mandatory that adequate amounts of exogenous thyroid hormone be administered to preclude the development of hypothyroidism. For it is in association with hypothyroidism that any remaining tumor receives its maximal growth stimulus. In the administration of exogenous thyroid hormone, it is probably wise to err on the side of over-treatment rather than under-treatment. There is no good evidence that the individual following total thyroidectomy is any more intolerant of excess amounts of exogenous thyroid hormone than those with part or all of their normal thyroid gland. A tremendous individual variation exists in this regard with some individuals exhibiting symptoms of hyperthyroidism on slightly more than replacement doses of thyroid hormone and others showing no evidence of toxicity on four to five times the requirement to maintain their euthyroid state.

Summary

From observations on experimentally produced cancer of the thyroid in animals as well as man, it is apparent that the biologic potential of this neoplasm is not strictly autonomous but may be influenced by an environmental factor. Such a factor would seem to be comparable to the promoting factor which can be demonstrated in the development of experimental thyroid cancer, viz. thyrotropic hormone. In the application of this concept to the management of thyroid cancer, suppression of thyrotropic hormone has been accomplished by the administration of excessive amounts of desiccated thyroid or other thyroid hormones. The clinical response of patients with papillary and alveolar cancer of the thyroid has substantiated the hypothesis that thyroid tumors exhibit varying degrees of dependency during their development and growth. Consequently, both function and growth of thyroid cancer either primary or metastatic may be either inhibited or stimulated according to the relative level of thyrotropic hormone.

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