Laboratory Diagnosis of Thyroid Tumors

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ABSTRACT

Laboratory procedures available for aid in the differential diagnosis of thyroid tumors include serum hormone measurements, a variety of thyroid scanning procedures, ultrasonography and needle biopsy of the thyroid. Serum calcitonin measurements appear to be highly reliable indicators of the presence of medullary carcinoma of the thyroid gland. Thyroid scans using isotopes of iodide or technetium, thyroid echography or other non-invasive procedures can identify patients in whom the presence of thyroid carcinoma is unlikely. However, no available procedure short of biopsy and histological identification can positively identify a thyroid mass as a carcinoma.

The problem of non-operative diagnosis of carcinoma of the thyroid gland is part of the larger problem of the differential diagnosis of uninodular and multinodular goiter. The thyroid abnormalities that may result in those findings include a thyroid cyst, single or multiple adenomatous nodules, chronic thyroiditis and the several types of thyroid adenomas and carcinomas. It is clear that the single most important source of information needed for resolution of this problem is careful palpation of the thyroid gland and surrounding structures. In many instances, the nature of the thyroid abnormality and/or the presence of local or distant metastases makes the diagnosis of thyroid carcinoma obvious, and only histological confirmation is needed. In other instances, notably when the clinical finding is a solitary nodule of the thyroid gland, the application of various laboratory procedures may prove of value in helping to identify those patients in whom tissue diagnosis is necessary and those in whom it is not.

Before reviewing the laboratory procedures available for the evaluation of such patients, some generalizations concerning carcinoma of the thyroid gland in relation to the problem of uninodular and multinodular goiter may be made.

Using the simplest possible classification, there are four types of thyroid carcinoma; papillary, follicular, medullary and anaplastic. The varied clinical features, age incidence differences and natural course of these types will not be reviewed here. In post-mortem studies thyroid carcinoma may be found in as many as 2.1 percent of people with clinically normal thyroid glands, and nodular goiter is considerably more frequent. Higher incidence rates are found in people with clinically abnormal thyroids. In the surgical literature, the frequency of thyroid carcinoma in single thyroid nodules ranges from about 5 to 30
percent or more in some series and is also considerable though less in patients who have multinodular goiter. Contrasted to these figures are epidemiologic data, such as that found in Framingham, MA. In this study, 4.2 percent of the study population was found to have thyroid nodules at the beginning of the study. None showed evidence of malignancy at the end of a 15 year period and no new lesions proven to be thyroid carcinoma appeared in the study group during the 15 year study period. These data may be explained in two ways. One is that patients in whom surgery is done are selected for it because of certain clinical findings. There is much evidence that this is the case. The second is that a histologic diagnosis of carcinoma of the thyroid gland may not indicate the presence of a biologic carcinoma. The problem is further complicated by the lack of unequivocal evidence that early diagnosis of carcinoma of the thyroid gland in any of its forms materially alters survival. The indolent course of the more common types of thyroid carcinoma merely compounds the uncertainties outlined.

Nevertheless, the clinical problem remains. Patients who have thyroid nodules may justifiably be concerned about the nature of the disease and may possibly benefit from early diagnosis and therapy. The question to be considered here is whether or not any laboratory procedures are of value in identifying such patients. Available procedures for the study of such patients include various serum hormone measurements, radioisotopic and ultrasonographic scanning techniques and needle biopsy.

**Serum Hormone Measurements**

Serum thyroid hormone concentrations, when measured by specific techniques, are virtually always normal in untreated patients with thyroid carcinoma. The presence of elevated serum thyroid hormone concentrations (and hyperthyroidism) in patients with thyroid carcinoma has been found in only two situations. A small number of patients have been described who had thyroid adenomas resulting in hyperthyroidism and in whom small areas of carcinoma were thought to be present within the adenoma.4 Hyperthyroidism has also been occasionally described in patients with widespread thyroid carcinoma, usually of the follicular type.6 These tumors are so inefficient as hormone producers, however, that large masses of tumor must be present for hyperthyroidism to result.

In some patients with thyroid carcinoma, elevations in serum protein bound iodide concentrations have been found.15 Further studies showed that the increase was due to ioprotein with the electrophoretic mobility of albumin, and not to an increase in hormonal iodide, in these patients.

In the special case of medullary carcinoma of the thyroid, current evidence indicates that most, if not all, of these tumors secrete calcitonin.18 Elevated basal serum calcitonin concentrations and/or exaggerated serum calcitonin increases after calcium infusion are extremely sensitive indicators of the presence of medullary thyroid carcinoma, as times indicating the presence of this tumor in the thyroid gland of patients without palpable thyroid abnormalities. Some tumors of this type also produce additional substances, such as serotonin, ACTH, prostaglandins and histaminase. Medullary carcinoma of the thyroid may also occur in association with pheochromocytoma and/or parathyroid hyperplasia (Multiple Endocrine Adenomatosis, Type II); one or another of these findings may be present in many family members. Therefore, findings of these latter disorders in a patient who has a thyroid mass, or his relatives, is strongly suggestive of medullary carcinoma of the thyroid.
Radioisotope Uptake and Scanning of the Thyroid Gland

**Iodide Isotopes and Pertechnetate**

The ability of thyroid tissue to actively transport iodide inwardly and incorporate it into thyroid hormones is the unique feature of this tissue. The availability of various isotopes of iodide and suitable techniques for the localized identification of these isotopes have made the thyroid scan an important tool for the evaluation of nodular disease of the thyroid gland. Since, as pointed out previously, hyperthyroidism is so infrequent in patients with thyroid carcinoma, quantitative measurements of uptake are of little value in the problem under consideration here.

Thyroid scans may be obtained using any gamma photon emitting isotope of iodide, but usually $^{131}$I-iodide or $^{125}$I-iodide are used for this purpose. Each has advantages and disadvantages in terms of clarity of the scans obtained, radiation dosage and visualization of retro-sternal thyroid tissue. The maximal accumulation of these isotopes in the thyroid gland usually occurs about 24 hours after their administration; thus, optimal resolution in thyroid scans is obtained at this time. $^{99m}$Tc-Pertechnetate, which, like iodide, is transported into the thyroid gland but is not further utilized, has recently found considerable favor as a thyroid scanning agent. Since pertechnetate is not further utilized by thyroid tissue, it diffuses out of the thyroid gland rapidly. The peak uptake of pertechnetate thus occurs within 30 minutes after its administration, and scanning must be done at this time. This is a convenience, particularly for outpatient work. The disadvantage of pertechnetate is that the ratio of thyroid to surrounding tissue radioactivity is much less than with isotopes of iodide; thus, resolution is less good. Nevertheless, pertechnetate and iodide generally yield similar results, though exceptions have been described. No matter which of these isotopes is used for thyroid scanning, satisfactory results cannot be obtained in a patient who has recently received iodides or any iodide-containing compounds.

Thyroid radioisotope scans allow recognition of the ability of the thyroid glands, or portions thereof, to accumulate isotope. The minimum size lesion that can be detected is about one cm. The fact that such accumulation does or does not occur need not correlate with the ability of the thyroid tissue to synthesize thyroglobulin and thyroid hormone, though obviously the thyroglobulin will be poorly iodinated and little thyroid hormone formed in thyroid tissue that concentrates iodide only poorly. In practical terms, a thyroid nodule or nodules are generally considered to be hyperfunctional ("hot"), isofunctional ("warm") or hypofunctional ("cold") by comparing their activity to that of the remainder of the thyroid tissue present. It is important to remember, however, that a misleading picture can be obtained if a hypofunctioning nodule is superficially or posteriorly located if normally functioning tissue is anterior or posterior to it. For this reason it is critical that the palpatory findings be carefully compared with those resulting from the thyroid scan.

What is the value of thyroid scan in the diagnosis of carcinoma of the thyroid? One important result is that often what is thought to be a single thyroid nodule on physical examination is revealed by the scan to be a gland containing multiple nodules. The likelihood that such a gland contains carcinoma is clearly less than when the nodule is indeed single. A second valuable result is the demonstration that a thyroid nodule is hyperfunctional. Since such nodules have been only very rarely found to contain carcinoma, this finding effectively excludes that diagnosis. However, only a small proportion (10 to 25 percent) of thyroid nodules are hyper-
functional. The remainder are about equally divided between iso- and hypo-functional nodules. Similarly, current experience shows that iso-functional nodules only rarely contain carcinoma. Thus, thyroid carcinoma is most likely to appear on the scan as a hypofunctional nodule. This need not imply the carcinoma cannot concentrate iodide at all, as there is evidence that most differentiated thyroid carcinomas can do so to some degree. Nevertheless, only a minority of solitary nodules that are hypofunctional are histologically malignant, the percentage being about 10 to 25 percent in most reports. The remainder, and majority, of these lesions are thyroid adenomas, adenomatous nodules or cysts.

**75Se-Methionine Scanning**

It has been shown that uptake of 75Se-methionine by neoplastic tissue is sufficiently greater than that of normal tissue to permit tumor localization by external scanning methods. Experience with this agent in the recognition of carcinoma of the thyroid gland is limited. Positive scans have been found in a number of thyroid carcinomas but it appears that benign tumors are equally likely to concentrate the 75Se-methionine. Since negative scans have also been found in patients with either benign or malignant thyroid tumors, it is clear this procedure is not a reliable one.

**Fluorescent Thyroid Scanning**

Fluorescent imaging of the thyroid is another new technique that has been applied to this problem. In this procedure, an exciting beam of photons from an 241Americium source are directed toward the thyroid gland. These photons, interacting with thyroidal iodide, result in production of characteristic X-rays which may be externally detected. This procedure has the advantages of not requiring administration of radioisotopes to the patient and low radiation dosage. Fluorescent thyroid scans can be performed in patients with an expanded extracellular iodide pool and those receiving thyroid therapy, both situations which result in little thyroidal uptake of iodide or pertechnetate. This procedure, in effect, measures the quantity of iodide in the thyroid gland or portions therein. Thus, nodules that are hypofunctional in terms of iodide uptake, should, and do, appear as non-iodide containing areas on the fluorescent scan. While no reports are available concerning the utilization of this procedure in patients whose lesions were studied histologically, it is apparent that this procedure is not likely to aid in the differentiation of benign and malignant hypofunctional thyroid nodules.

**Thyroid Echography**

Ultrasoundography has recently been applied to the investigation of thyroid disease. When ultrasound impulses are applied to the neck, most of the sound passes through the tissues but a certain proportion is reflected back to the surface. A homogeneous structure such as a cyst transmits the sound without any echoes except for those generated at the tissue-fluid interfaces. Thus, the most useful application of this procedure is for the recognition of cysts of the thyroid. It appears that echography is quite reliable for this purpose. In a recent report, all cystic lesions so recognized were found to contain no evidence of malignancy when the aspirated cyst fluid was examined cytologically. Furthermore, none of the nodules that proved to be carcinoma had the echographic appearance suggestive of cystic lesions. As is the case with other outlined procedures, however, echography will probably not have value in the identification of the pathological nature of solid lesions.

**Needle Biopsy of Thyroid Nodules**

Aspiration biopsy of thyroid nodules has not been widely employed in the past for
several reasons. One has been a fear that a biopsy of a malignant lesion would result in spread of the tumor. Secondly, adequate specimens have not always been obtainable and this has posed a special problem in thyroid tissue because of the heterogeneity of thyroid carcinoma. Recently, there has been renewed interest in this technique. These reports have not suggested that the procedure results in a significant number of incorrect diagnoses. Needle biopsy, or rather aspiration, is usually effective therapy for a thyroid cyst.

Conclusions

It should be clear that there is no single laboratory procedure, short of biopsy, which will allow certain diagnosis of the various diseases that produce nodular lesions of the thyroid gland. Medullary carcinoma of the thyroid appears to be an exception, but this type of tumor constitutes only a small proportion of all thyroid carcinomas. Certain findings obtained by scanning and/or echography clearly serve to identify patients whose lesions are very unlikely to be carcinomas of the thyroid. No scanning procedure can positively identify a thyroid lesion to be a thyroid carcinoma. However, by a combination of clinical and laboratory procedures, patients can at the least be divided into high and low cancer-risk groups and the number of patients in whom operative diagnosis is needed be greatly reduced.

References

The First Abraham J. Gitlitz Memorial Lecture was given by
Dr. Klaus Schwartz* at the 45th Meeting of the Association of Clinical
Scientists on March 9, 1974, La Jolla, California

An abstract of Dr. Schwartz's lecture follows. Abstracts of the other scientific papers presented
at the meeting will be published in the next issue of the Annals.

**Elements Newly Identified as Essential for Animals**

In contrast to the 11 elements of low atomic weight which constitute the bulk of living matter, essential trace elements are effective in very small amounts. They are always linked to organic compounds by coordination or covalent bonds. Through special physiochemical conditions, they are able to fulfill highly specific functions, playing a decisive role in life. The principal parameters and dimensions which characterize the role of trace elements in health and disease processes are illustrated, using as examples some elements recently discovered to be indispensable. Until 1957 only seven elements were proved essential in animals and man: iron, iodine, manganese, copper, zinc, cobalt and molybdenum. In 1957 selenium was added. Chromium (III) was established to be essential for glucose utilization in 1959. Subsequently, highly purified, chemically defined amino acid diets and trace-element "sterile" isolator techniques were developed. By this approach, tin was recognized in 1970, and vanadium in 1971, to be necessary for growth in the rat, followed by the demonstration that fluorine is essential for growth and development, aside from its effects on teeth and bone. Two other elements, silicon and nickel, may be required, but proof for their essentiality is not yet rigid. Thus, a number of elements have been newly demonstrated to be indispensable. Selenium serves to illustrate that vastly different deficiency diseases in different species are caused by lack of a specific trace element and that various compounds of an element can have very different potencies. Chromium shows that deficiency of an essential trace element may produce only minor but clinically important changes and that valence states show different biological activity. Hexavalent chromium is inactive; only trivalent and possibly bivalent chromium are biologically useful. Thus, determination of an element in diets, tissues or blood does not constitute an estimate of biological activity. To determine availability, nutritional balance studies and biological assays are unfortunately needed. Tin serves as an example of an element for which no biological function was known before it was recognized to be essential for mammalian growth. Vanadium, on the other hand, was suspected for years to have biological and clinical importance, but the crucial experiment with animals could not be done until recently. Trace elements, aside from their toxicological effects, play a major role in disease mechanisms if there is too little, too much (imbalance) or if there are disturbances in their utilization and metabolism. Highly specific mechanisms are frequently used in absorption and handling of trace-element supplies and of essential elements in blood plasma. Often, there are storage mechanisms, such as ferritin for iron, thyroglobulin for iodine and fluoroapatite for fluorine. Other elements, such as vanadium and possibly tin, are stored in fat tissue. While some older trace elements are connected with well-known clinical disease entities, such as iron-deficient anaemia and goitre owing to lack of iodine, others are not yet connected with specific diseases. It may be expected that some of the newly essential elements may eventually be of clinical importance. Areas where trace-element function may be implicated etiologically are atherosclerosis, cerebral arterial disease, cancer, cardiomyopathy, muscular dystrophy, some degenerative diseases of the central nervous system and possibly even some diseases as common as degenerative osteoarthritis.

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