

Chapter 9

THE CLINICAL UTILITY OF FLUORESCENT SCANNING OF THE
THYROID

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I. INTRODUCTION

In 1964 Heedman and Jacobson¹ first quantitated human stable thyroidal iodine by in vivo X-ray spectrometry. Hoffer²⁻⁴ initially used Dysprosium-159 (Dy-159) and a lithium-drifted silicon crystal in a low temperature vacuum chamber to image the thyroid by FEA. The energy of ¹⁵⁹Dy radiation was above the K-shell binding energy of stable iodine and the characteristic X-rays produced in filling the resulting orbital vacancies could be detected externally. Americium sources proved more advantageous in later studies and attachment of the fluorescent apparatus to medical rectilinear scanners produced satisfactory thyroid images and demonstrated the size, shape, and positional relationships of the thyroid lobes. This method produced satisfactory localization of palpable thyroid nodules. A particular advantage of the fluorescent technique is the absence of whole body, gonadal, or bone-marrow radiation and the absence of radiation to the fetus of pregnant women.

More recently, fluorescence excitation has been used to quantitate stable intrathyroidal iodine.⁵⁻⁸ These studies have indicated slight sex and age differences in stable

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iodine content, have initiated the study of the relationship of this iodine mass to thyroid physiology, and have produced clinically useful data in various thyroid disorders. Summarized results from thyroid stable iodide quantitation in a large number of patients with common thyroid diseases are shown in Table 1.

II. THE NORMAL FLUORESCENT THYROID SCAN

The types of images obtained from fluorescent thyroid scanning are indistinguishable from those of isotope scanning, since the same electronics and data presentation systems are used. The size, shape, and positional relationships of the thyroid lobes are therefore comparable to isotope scanning, with the right lobe larger in the majority of normal cases, the two lobes of equal size in a smaller number, and the presence of a larger left lobe in a still smaller number. In our system, the ratio of target-to-background count rates is approximately 20 to 1 when the normal thyroid gland is compared to extrathyroidal cervical count rates. The background count rate is due to scatter, the semiconductor detector, and system electronics rather than actually detectable nonthyroidal stable iodine, since the stable iodine content of both nonthyroidal human tissue and blood is extremely low. With regard to iodine quantitation, we have found that the mean value of glandular stable iodine in normal males is approximately 10 mg and the mean female level approximately 9 mg (Table 1). The significance of this apparent difference is unknown, but there are no clinically significant differences between thyroid function as inferred from levels of thyroidal radioiodide uptake, serum thyroxine, serum triiodothyronine, and serum thyrotropin (TSH) between groups of normal males and females. Patton et al.⁸ found a mean thyroidal stable iodine of 10.7 ± 4.8 mg in a group of normal persons.

Satisfactory studies can usually be performed in normal individuals taking fully suppressive doses of thyroid medication (2 gr of desiccated thyroid or 0.2 mg of sodium-levo-thyroxine daily) if the period of medication is brief, 4 weeks or less, but in normal persons on long term doses of this magnitude (three months or longer), intrathyroidal stable iodine levels are usually very low and fluorescent thyroid scans generally unsatisfactory. Our initial studies indicate that the mean value of thyroidal stable iodine may decline somewhat with age, but the clinical significance of this finding is unclear at present. In a series of normal patients, there was no significant correlation of glandular stable iodine content with thyroidal isotope uptake, serum thyroxine, serum tri-

TABLE 1

Stable iodine levels detectable in the thyroid glands of consecutive patients with various thyroid disorders

	Number	Range	Mean	S.D.
Normal				
Female	41	4.1—19.0	9.2	4.3
Male	26	3.8—17.5	9.9	4.5
*Graves disease	68	6.2—28.0	15.5	7.8
*Nodular goiter	53	4.1—20.0	11.7	5.6
*Hashimoto's thyroiditis				
Euthyroid	56	ND—18.0 ^b	4.8	3.7
Hypothyroid	13	ND—5.2 ^b	2.3	2.0
Secondary hypothyroidism	4	6.1—10.6	9.1	2.0

* 80—90% Female in each of these groups.

^b ND = Not detectable

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iodothyronine, or the serum ratio of the two latter hormones. We have noted no racial differences comparing Caucasian, Negro, and Chinese patients living in North America.

III. GRAVES' DISEASE (DIFFUSE TOXIC GOITER)

In cases of hyperthyroid Graves' disease, the total thyroidal stable iodine content is generally increased in proportion to size of the patient's goiter, implying a concentration of stable iodine which is not greatly different from normal values. Patton and co-workers⁸ also described increased glandular iodine in hyperthyroid patients, the latter presumably representing Graves' disease. Euthyroid patients with the ophthalmopathy of Graves' disease behave differently in this respect than patients with hyperthyroidism alone, in that glandular stable iodine levels range from below normal (but detectable) to slightly above the mean normal. The significance of this finding is presently uncertain, but abnormalities of thyroid function, including failure to suppress when treated with exogenous thyroid medication, and flattening of the pituitary response to thyrotropin-releasing-hormone (TRH) are well documented in this group of patients.⁹⁻¹⁰

Patients with surgically treated Graves' disease and euthyroid function usually have normal or low glandular levels of stable iodine, and in patients who are hypothyroid after such surgery, levels are generally low or undetectable. Levels are also usually low or undetectable in patients rendered hypothyroid by therapeutic NaI,¹³¹ and low or normal in the patients remaining euthyroid after this form of surgery.

Figure 1 shows a patient with hyperthyroidism due to Graves' disease in which the fluorescent scan shows normal stable iodine as a result of previous treatment with Propylthiouracil.

There is some tendency for patients with low levels of glandular iodine to have increases in the ratio of serum triiodothyronine to serum thyroxine in Graves' disease, perhaps indicating some ability of the thyroid gland to conserve iodine by a change in relative secretion of the two hormones.

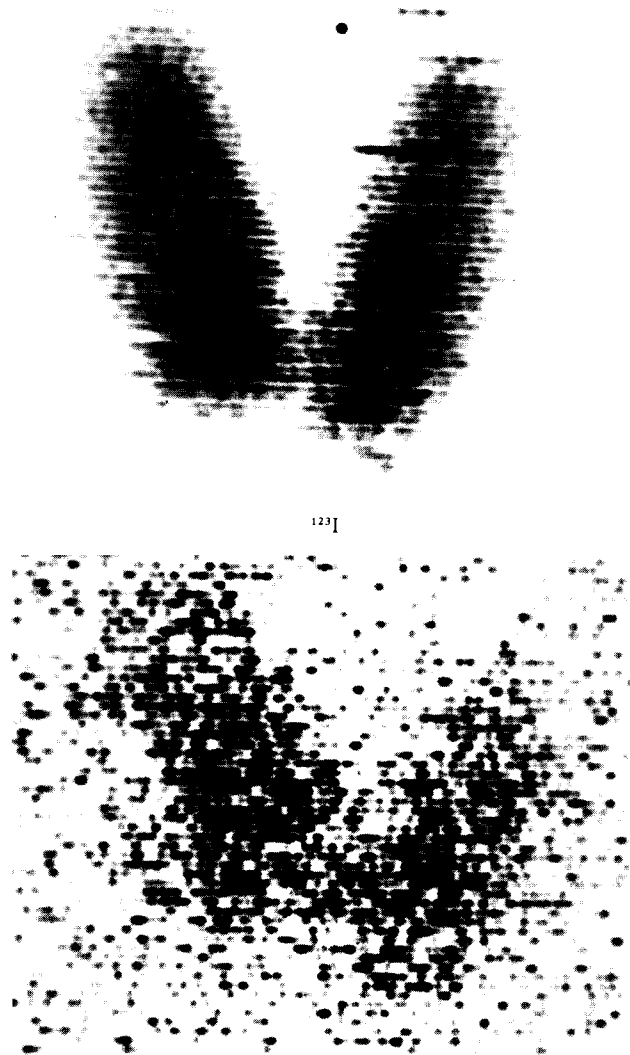
Figures 2 and 3 show two patients treated, respectively, with surgery and therapeutic radioiodide, both of whom show satisfactory isotope scintigrams, but with glandular iodide depletion shown on the fluorescent study. Both situations are compatible with rapid turnover of a small glandular iodine pool.

IV. NONFUNCTIONING NODULES

Thyroid nodules found in this laboratory to be nonfunctioning by imaging with sodium ¹²³I or Tc-99m pertechnetate have invariably contained no detectable stable iodine by the fluorescent technique. Since the resolution obtained by these methods is of the order of 1 cm, it appears in most cases unwarranted to attempt resolution of very small nodules by the fluorescent technique instead of conventional isotope scanning. We have observed no differences between benign and malignant thyroid nodules by this technique, nor in the total iodine content of the glands from which they arise. Hoffer^{3,4} also found no stable iodine in both benign and malignant nonfunctioning nodules. The resolution achieved also makes fluorescent thyroid scanning a poor method of searching for functioning thyroid carcinoma since the stable iodine content of this tissue is low in relation to normal tissue, and the lesions tend to be located deep in cervical lymph nodes, or in other poorly accessible locations such as mediastinum, lung, or bone.

V. FUNCTIONING THYROID NODULES

Nodules found to be functioning with radioiodide or pertechnetate contain stable



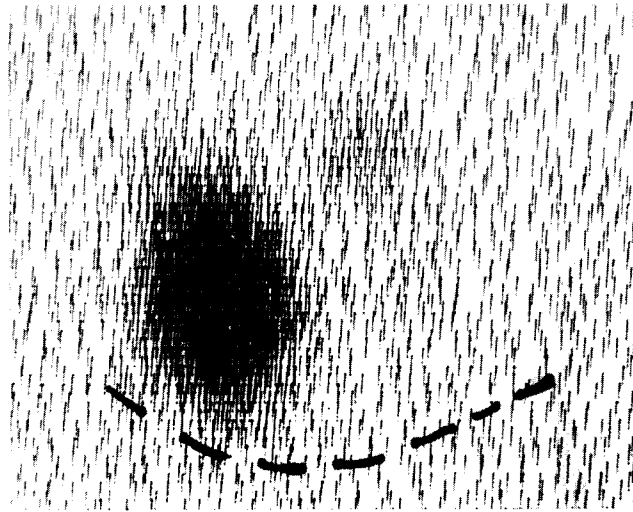
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FIGURE 1. Thyroid imaging studies on a 27-year-old female with active Graves' disease despite treatment with propylthiouracil until the day before. She had diffuse thyroid enlargement, a 24-hr thyroidal radioiodide uptake of 100%, and a serum thyroxine of $17\mu\text{gdl}$. Recitilinear scintigram (^{123}I) is shown on the left. The fluorescent scan on the right shows a normal stable iodine level of 11 mg, a normal value probably as a result of blockade of iodide organification by antithyroid drug.

iodine in almost all cases, and this content is generally in proportion to the amount of tissue mass present. Large single autonomous thyroid nodules may contain as much as 10 to 15 mg total stable iodine when studied by this technique. In hyperfunctioning nodules with functional suppression of surrounding or contralateral thyroid tissue, the latter tissue cannot usually be located or documented by fluorescent imaging.

Both functioning and nonfunctioning nodules (if greater in largest diameter than approximately 1 cm) can be marked *in vivo* under the detector for unambiguous localization and correlation with physical location.

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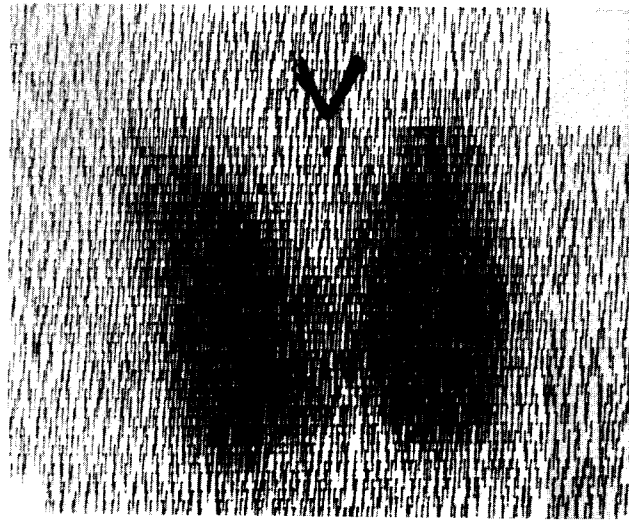
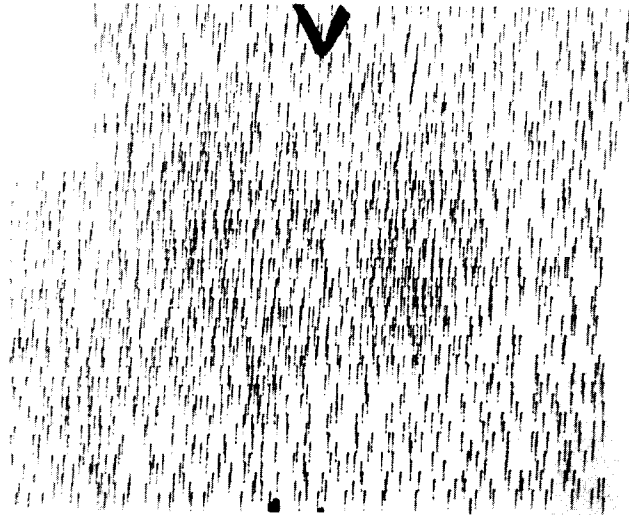
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FIGURE 2. Thyroid imaging studies on a 54-year-old female who had surgery for Graves' disease 24 years previously, and recently developed symptoms suggestive of hypothyroidism. A small amount of thyroid tissue was palpable in the neck. Serum thyroxine was low at 4.7 ug/dl, but serum triiodothyronine was normal at 165 ng/dl. Thyroidal radioiodide uptake at 24 hr was low normal at 14%. Isotope scan (¹²³I) showed functioning tissue in a residual right lobe and possibly a pyramidal lobe, but fluorescent scan showed less than 1.5 mg stable iodine. Rapid turnover of intrathyroidal iodine was demonstrated by labelling the thyroid with ¹³¹I.

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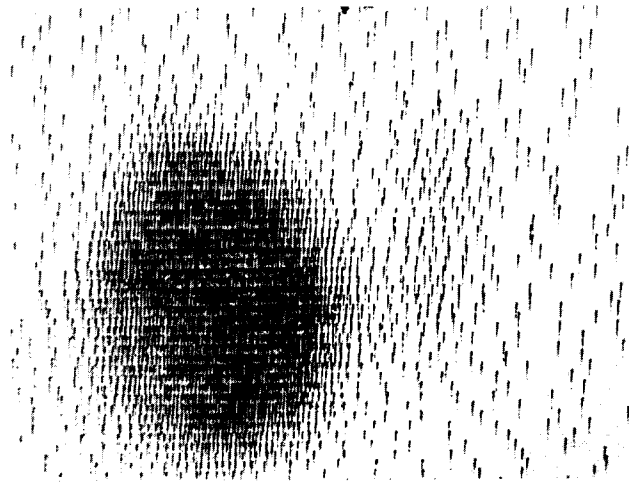
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FIGURE 3. Thyroid imaging studies on a 30-year-old male with persistent Graves' disease despite treatment with therapeutic sodium iodide-131 6 months previously. Serum thyroxine was elevated at 17.8 ug/dl and 24-hr thyroidal radioiodide uptake persistently elevated at 46%. Rectilinear scintigram with ¹²³I is shown on the left. The fluorescent scan indicated the presence of only 1.7 mgm stable iodine in the gland, although the level had been greatly elevated (28 mg) before radioiodide therapy.

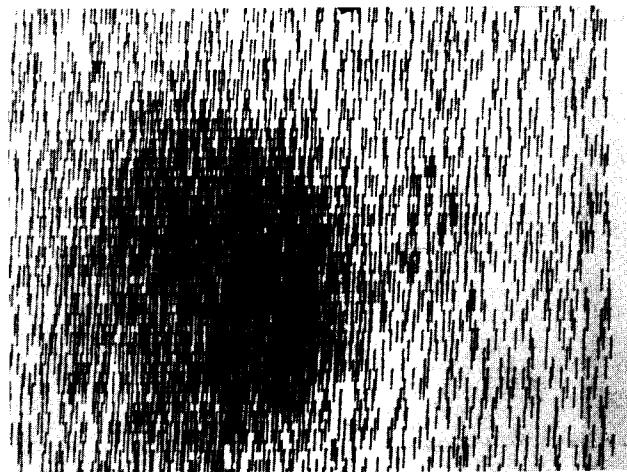
Figure 4 shows isotope and fluorescent scans from a patient with a large autonomous hyperfunctioning thyroid nodule, showing two very similar images.

VI. HASHIMOTO'S THYROIDITIS

Total thyroidal stable iodine content is decreased in many cases of Hashimoto's thyroiditis and undetectable in some of these. Whether this is due to actual destruction of tissue or kinetic abnormality of iodine metabolism is uncertain at present and may even differ among various types of glands. Values tend to be particularly low in patients with hypothyroidism of this etiology, but may be below normal (although very



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FIGURE 4. Thyroid imaging studies in a 23-year-old female with hyperthyroidism due to a large autonomous adenoma occupying most of the right lobe. Serum thyroxine was elevated at $21 \mu\text{g}/\text{dl}$ and 24-hr thyroidal radioiodide uptake was 79%. Both the isotope (^{123}I) and fluorescent scans show a functioning nodule, but no evidence of the contralateral suppressed lobe, which was palpable clinically.

low on a concentration basis) in patients with goiter without hypothyroidism. We have noted no differences in relation to age, sex, or the presence of a positive family history of the disease in thyroiditis patients. The presence of a negative correlation between total glandular iodine content and the serum ratio of triiodothyronine to thyroxine may indicate some ability to conserve glandular iodine in this disease. However, no relationship has been established between total glandular iodine content and thyroidal radioiodide uptake.

A very low thyroid stable iodine content in a hyperthyroid patient renders secondary (pituitary) hypothyroidism unlikely, as thyroidal stable iodine content in that disorder is usually normal in our experience.

Figure 5 shows a satisfactory isotope scan from a patient with Hashimoto's thyroiditis whose fluorescent scan was unsatisfactory because of iodide depletion. The latter provided diagnostic information. However, Figure 6 shows a normal isotopic and normal fluorescent scan in secondary hypothyroidism. In contrast, Figure 7 illustrates the poor radioiodine uptake and equally poor ^{123}I scan in a patient with subacute thyroiditis whose fluorescent iodine scan was normal.

VII. NODULAR GOITER IN NORTH AMERICA

In almost all cases of this disease, the total glandular iodine content is normal or slightly elevated, although the iodine per gram of tissue must be decreased in the majority of these cases since the thyroids are characteristically enlarged. Levels appear roughly correlated with gland size, however, and appear no different in cases associated with nonfunctioning or functioning nodules of moderate size or less. We have noted no relationship between glandular stable iodine and serum triiodothyronine-to-thyroxine ratio in nodular goiter.

Fluorescent thyroid scanning is generally inferior to the isotopic technique (particularly the use of sodium ^{131}I) for localization of substernal goiters, since the linear attenuation coefficient for the iodine characteristic X-ray is very high and interposed bone renders its consistent detection unlikely. The stable iodine content of large nodular goiters is frequently irregular in distribution, and the ability to identify and localize small nodules is much less satisfactory than higher resolution techniques, such as pin-hole gamma camera imaging after intravenous injection of Tc-99m pertechnetate.

VIII. RADIATION-INDUCED THYROID DISEASE

We have previously described a tendency toward low levels of total thyroidal stable iodine in patients who had incidental radiation to the thyroid gland when receiving head or neck radiation for acne, tonsillitis, or thymic enlargement early in life.¹¹ This group of patients has been of intense interest to thyroidologists because of the high prevalence of thyroid tumors (both benign and malignant) arising many years after radiation in childhood or adolescence.¹²⁻¹⁴ In some of these radiation cases, the patients are found to have Hashimoto's thyroiditis, and the glandular iodine depletion may be on that basis. In other cases, this disease appears not to be present and no precise explanation is known. Since pituitary thyrotropin (TSH) is implicated in the development of most thyroid tumors,^{15,16} and the iodide depleted thyroid gland is known to be physiologically more sensitive to TSH,¹⁷ any glandular iodide depletion caused by radiation might be clinically significant in the development of tumors in these patients and deserves further study.

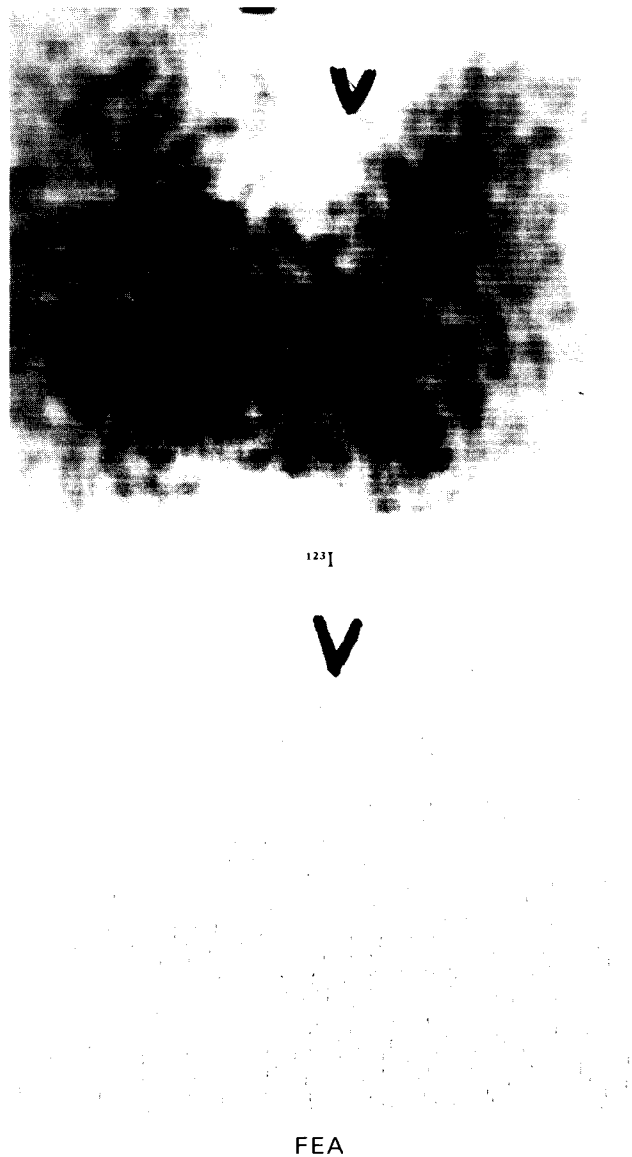
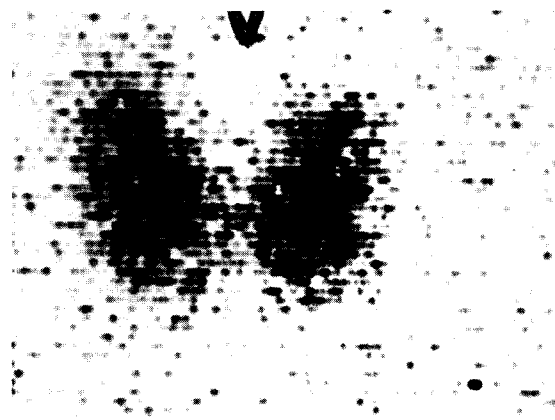


FIGURE 5. Thyroid imaging studies on a 56-year-old female with goitrous hypothyroidism. Serum thyroxine was low at $2.6 \mu\text{g}/\text{dl}$ and 24-hr thyroidal radioiodide uptake normal at 28%. Thyroglobulin and microsomal antibodies were both present in high titer in the serum. Rectilinear scintigram (^{123}I) showed glandular enlargement, but fluorescent excitation scan showed no detectable stable iodine. The final diagnosis was Hashimoto's (chronic lymphocytic) thyroiditis.

IX. THE FUTURE OF FLUORESCENCE EXCITATION IN THE STUDY OF THYROID PHYSIOLOGY

Future developments in excitation sources, semiconductor detectors, and electronics may result in improvement in the results now available with fluorescence excitation studies of the thyroid gland. Increases in resolution and sensitivity may also increase the diagnostic yield regarding small thyroid nodules. Even a two-to-four-fold improvement in realizable resolution would produce thyroid images demonstrating thyroid



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FIGURE 6. Thyroid imaging studies on a 25-year-old female with clinical signs of hypothyroidism, amenorrhea, and a chromophobe adenoma of the pituitary gland. Serum thyroxine was low at $5.1 \mu\text{g}/\text{dl}$ and serum TSH only $3\text{mU}/\text{ml}$ despite hypothyroidism; 24-hr thyroidal radioiodide uptake was low normal at 12% and rectilinear scintigram (^{123}I) was normal. The normal fluorescent scan and stable thyroidal iodine levels provided evidence that the hypothyroidism was pituitary in origin.

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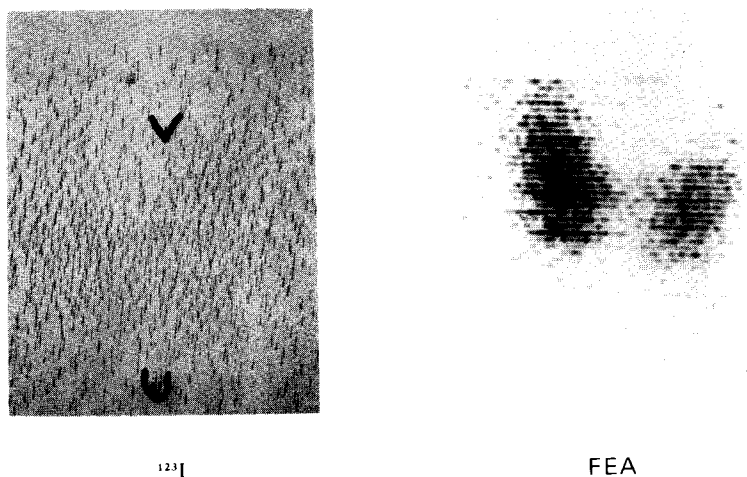


FIGURE 7. Thyroid imaging studies on a 51-year-old male with fever, painful thyroid enlargement, and symptoms of hyperthyroidism. The gland was modestly enlarged and very tender. Serum thyroxine, triiodothyronine, and thyroglobulin were all elevated. Thyroidal radioiodide uptake was below detectable levels and isotope scintigram (^{123}I) not satisfactory. Fluorescent scan was normal, however.

nodules much smaller than those palpable clinically in normal-sized thyroid glands. Such improvements would be even more helpful for nodules palpable with great difficulty in goitrous glands.

Application of these techniques to the world-wide problem of iodide deficiency goiter is expected, and may prove useful in the study of the efficacy of various dietary or parenteral methods for iodide supplementation for whole human populations. In more industrialized countries, where dietary iodide intake has greatly increased in recent decades, the future viability of isotopic thyroid imaging may come into question as the normal level of radioiodide uptake falls, and may result in even greater interest in FEA techniques.

Fluorescence excitation has already become the method of choice for thyroid imaging during pregnancy and lactation, in pediatric patients capable of cooperating during the imaging study, and in the large number of hospitalized patients undergoing thyroid imaging studies after administration of iodides as contrast media or medicinals. Such clinical uses will no doubt be exploited widely.

The finding that previously irradiated thyroid glands are sometimes iodide depleted, coupled with the observation that the iodide depleted gland in experimental animals is physiologically more sensitive to the effects of pituitary thyrotropin (TSH), may lead to changes in the understanding of radiation-induced thyroid disease and to changes in the clinical management of at least some of these patients, who are known to be at high risk for thyroid tumor development.

The lower levels of stable thyroidal iodine found in some elderly patients without other evidence of thyroid abnormality may lead to additional understanding of thyroid physiology in old age. For example, it may explain the common observation of a gradual enlargement of the gland with age, which is often seemingly unassociated with clinically demonstrable physiologic disturbance.

It also appears rational to study in a comprehensive manner the possible clinical usefulness of fluorescence excitation to quantitate stable glandular iodine in the course of prolonged antithyroid therapy of diffuse toxic goiter (Graves' disease) with antithyroid drugs. The untreated disease is characterized in most cases by increased total iodine stores, and the thiourylene drugs are known to interfere with thyroid hormone

production by blockade of iodide organification. The demonstration of satisfactory organification blockade by fluorescence excitation appears feasible now, and may lead to some prognostic measure for selecting patients whose disease has achieved remission, or selecting those failing to remit for subsequent definitive treatment by surgery or sodium radioiodide. It now also appears feasible to relate the total glandular stable iodine content in Graves' disease to levels of glandular hormone on digests of thyroid tissue as determined in vitro after surgery; to study the interrelations of total glandular iodine level, glandular thyroxine, and triiodothyronine level; and to relate these quantities to the respective serum levels of thyroid hormones.

Study of the relationships of thyroidal stable iodine content to relative secretions of thyroxine and triiodothyronine and their secretion rates can be expected to clarify the roles of these two compounds in human physiology.

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