Differentiation of Malignant from Benign Lesions of the Thyroid Gland Using Complementary Scanning with ^{75}Selenomethionine and Radioiodide

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THE physical characteristics of thyroid cancer are similar to those of nodular goiter. In the absence of obvious invasion or metastatic disease differentiation can frequently be made only by histologic examination. Radioiodide scan has identified functioning and hyperfunctioning nodules, however, most thyroid nodules are nonfunctioning, representing adenomatous goiter, cysts, nonfunctioning adenomas, localized thyroiditis or cancer. The majority of nodules removed because of the possibility of thyroid cancer are benign.[9, 11, 13, 14, 16] In view of the high incidence of nodular goiter in the adult population the need for better preoperative methods of diagnosis of thyroid cancer is obvious.

Malignant lesions of the thyroid have three unique characteristics, viz., a relative inability to trap iodide, an increased rate of cell replication, and a high degree of cellularity. Considered conjointly these characteristics may be used to differentiate malignant from benign disease. Furthermore, these properties may be appraised by appropriate thyroid scanning technics. In the euthyroid patient rarely is there a selective uptake of iodide by even a well differentiated malignant tumor. ^{75}Selenomethionine on the other hand may be concentrated by a malignant tumor since it is incorporated into cells according to the rate of protein synthesis.[1, 2] The uptake of this isotope in tissues undergoing more rapid rates of anabolism, e.g., liver,[8] pancreas,[8] parathyroid adenoma,[5] thymoma,[17] and lymphoma[7] is sufficient to permit identification by external counting technics. ^{75}Selenomethionine uptake in the normal thyroid is low although it can be altered by thyroactive substances and thyrotropin.[15] This investigation reports the feasibility of utilizing both radioiodide and ^{75}Selenomethionine as complementary scans to provide a more reliable method of differentiating malignant from benign lesions of the thyroid.

Methods

Patients over the age of 40 in whom there was a suspicion of thyroid cancer were evaluated preoperatively by photoscans with radioiodide and ^{75}Selenomethionine (Table 1). One hundred fifty to 250 μc. of ^{75}Selenomethionine (3 μc. per Kg. of body weight) were administered intravenously and a thyroid scan performed at

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15 and 60 minutes. The specific activity of the ^{75}Selenomethionine ranged from 70 to 400 millicuries per milligram (obtained from E. R. Squibb and Son as "Sethotope"). ^{75}Selenomethionine has a physical half life of 128 days and a biologic half life of 23 days. The principal gamma ray energy is 0.269 Mev. A total body dose after the standard scanning dose of 3 μc. per Kg. of body weight is 0.9213 rads with an additional 0.06 rads to the pancreas and 0.05 rads to the liver. No adverse reactions to ^{75}Selenomethionine have been reported. Scans were recorded with a Picker magnascanner with a 3 inch sodium iodide crystal 230–330 kev. window, 0.15 centimeters line spacing, 19 holes Picker-moderate focus collimator.

Scans with radioiodide were made in conjunction with the determination of a 6 and/or 24 hour uptake of 50 to 100 μc. of ^{131}Iodine. Sequential scans with ^{75}Selenomethionine and radioiodide were frequently performed within the same 7 to 25-hour period. If the ^{131}Iodine scan precedes the ^{75}Selenomethionine scan with there being residual ^{131}Iodine within the gland interpretation is much more difficult. (Fig. 1).

Scanning may be performed sequentially with either radioiodide or ^{75}Selenomethionine by taking advantage of the different energy spectra of the radionuclides available, i.e., ^{125}Iodine −0.035 Mev., ^{75}Selenium −0.269 Mev. and ^{131}Iodine −0.364 Mev. By using in sequence isotopes of increasing energy spectra scans with both radioiodide and ^{75}Selenomethionine may be made during a 7 or 25 hour period in conjunction with a 6 and/or 24-hour uptake of radioiodide. In routine evaluation ^{125}Iodine is superior to ^{131}Iodine since with a functioning or hyperfunctioning nodule there is little need for a subsequent scan with ^{75}Selenomethionine. ^{125}Iodine is not suitable for determining uptake, however, the simultaneous administration of 3 to 5 μc. of ^{131}Iodine will provide sufficient activity within the gland for determination of uptake without interfering with subsequent ^{75}Selenomethionine scan.

TABLE 1. *Results of ^{75}Selenomethionine Scanning in Diseases of Thyroid*

Diagnosis	Positive	Indeterminate	Negative
Carcinoma (10)	8	2	—
Lymphoma (1)	1	—	—
Thyroiditis (5)	3*	2#	—
Adenoma (8)	5#	2	1#
Nodular goiter (22)	4#	2**	16**

(all were nonfunctioning ["cold"] by ^{131}I except as noted)

* Two-functioning by ^{131}I scan.
** One-hyperfunctioning by ^{131}I scan.
\# One-functioning by ^{131}I scan.

All scintigrams were evaluated independently for quantitative uptake in the area of the thyroid nodule and homogeneity of uptake elsewhere. Photoscans with ^{75}Selenomethionine were considered positive when there was sufficient concentration of the isotope above background to permit visual identification of its localization. The concentration was graded on basis of 1–4 (Table 2). A positive scan was usually associated with a concentration of radioactivity two to three times above background (Grade 2, 3, and 4). If there was definite uptake above background but without particular localization or merely a heterogeneous distribution the scan was considered indeterminate (Grade 1). When there was no uptake above background the scan was interpreted as negative.

Following microscopic examination of the "nodules" removed, the degree of cellularity was rated on the basis of 1 to 4, 1 being that of the normal thyroid gland and 4 that of a dense, compact, highly cellular tumor (Figs. 4, 5).

In surgical specimens containing ^{75}Selenomethionine (18 to 196/hours after administration of the isotope) the radioac-

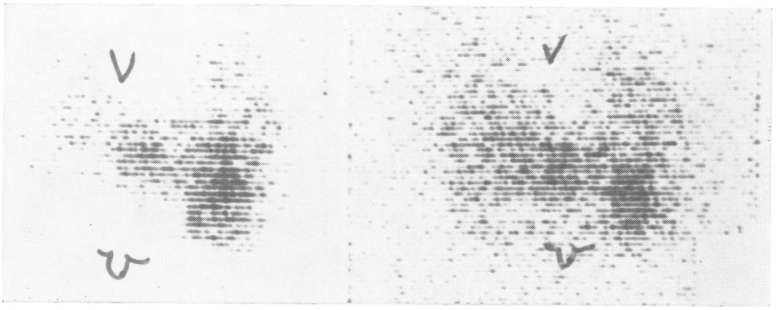

FIG. 1. (a) Complementary scans in a 75-year-old woman with a giant cell carcinoma involving the right lower pole of the thyroid. The ^{75}Selenomethionine scan (right) was performed 3 days after the administration of radioiodide and depicts both ^{75}Selenium and ^{131}Iodine. The tumor which was "cold" by radioiodide scan (left) demonstrates appreciable uptake of ^{75}Selenomethionine.

tivity of the "tumor" was compared with that of the normal thyroid and expressed as a ratio of counts per minute/mg. of wet tissue.

During the past 3 years complementary photoscans have been carried out in eleven patients with malignant tumors of the thyroid, five patients with thyroiditis, eight patients with follicular adenoma, and 22 patients with nodular goiter (Table 1). All diagnoses were based upon histologic examination.

Results

1. Malignant Tumors (Table 2)—eleven patients were evaluated, ten with adenocarcinoma and one with lymphoma (Figs. 1, 2, 3, 4, 5). None of the tumors selectively concentrated radioiodide and all would be considered as harboring "cold" nodules. Nine ^{75}Selenomethionine scans were regarded as positive and two as indeterminate. All of the tumors identified had one diameter of greater than two cm.

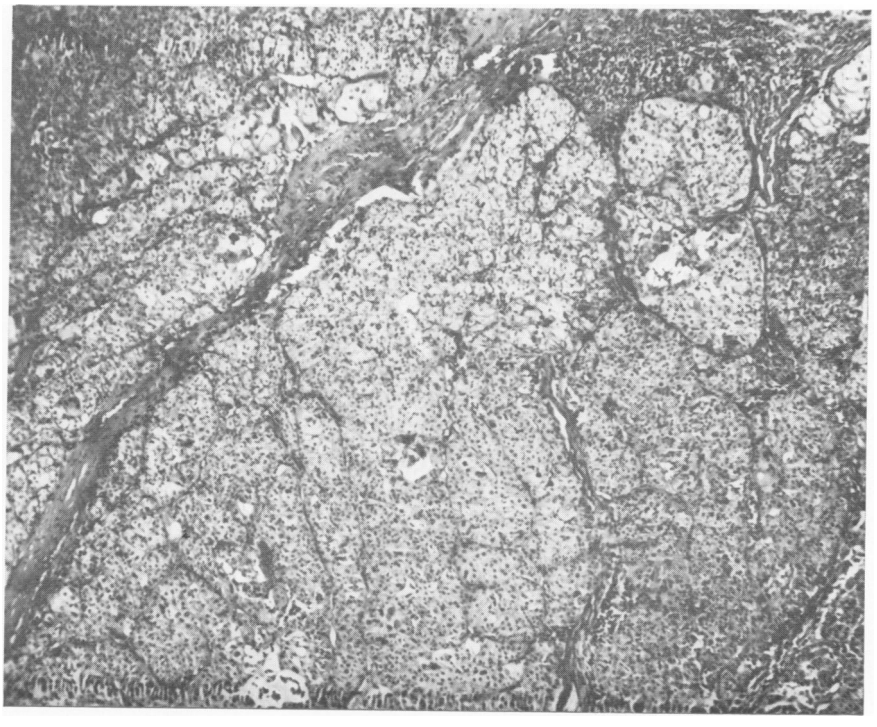

FIG. 1. (b) Photomicrograph. (Hematoxylin and eosin ×70.)

TABLE 2. *Uptake of Radioiodine and ^{75}Selenomethionine in Thyroid Cancer*

PT	Sex	Age	Diagnosis	Mass in Cm.	^{131}I	^{75}Se	Cell Density	Ratio (tumor:normal) (cpm/mg. wet)
H. V.	M	55	Follicular carcinoma	5 × 4.5 × 4	0	2	3	—
R. P.	M	57	Follicular carcinoma	4 × 3 × 2.5	0	1	3	1.7:1.0 (23)*
C. W.	F	75	Follicular carcinoma	5 × 4 × 3.5	0	4	3	1.3:1.0 (20)*
H. R.	F	45	Follicular carcinoma	2 × 1 × 1.6	0	3	2	—
N. M.	F	56	Papillary carcinoma	2.5 × 2.5 × 2.5	0	2	3	2.2:1.0 (1)*
I. C.	F	51	Papillary carcinoma	4 × 3 × 3	0	2	2	—
L. G.	F	47	Follicular and papillary carcinoma	3 × 2 × 2	0	1	2–3	—
A. B.	F	74	Giant cell carcinoma	5 × 5 × 2	0	2	3	—
B. K.	F	82	Small cell carcinoma	5 × 5 × 5 (cervical metastases)	0	4	4	—
M. S.	F	68	Malignant lymphoma	2.5 × 2.5 × 2.5	0	4	4	2.6:1.0 (18)*
P. B.	F	52	Undifferentiated carcinoma	5 × 5 × 5	0	4	4	—

Concentration of ^{75}Selenomethionine and ^{131}Iodine graded on basis of 1–4.
Cell density (degree of cellularity) appraised on basis of 1–4 (normal thyroid = 1, solid anaplastic tumor = 4).
* Hours after injection of ^{75}Selenomethionine.

The ^{75}Selenomethionine scan failed to localize an incidental carcinoma measuring 1.0 cm. in diameter in a patient with a follicular adenoma measuring 3 cm. in diameter (Fig. 7).

The ratio of radioactivity of tumor to normal thyroid as determined in the specimen varied from 2.6–1.3/1. This ratio was more likely to approach unity when there was a lymphocytic infiltrate within the gland. The most conspicuously positive scans occurred in a patient with a small cell adenocarcinoma with lymph nodes metastases (Fig. 4), and in a patient with a malignant lymphoma (Fig. 5). This latter patient had a minimal uptake of radioiodine and in view of the configuration of the thyroid being maintained these scanning characteristics would be most consistent with Hashimoto's thyroiditis.

Two additional patients with metastatic thyroid cancer in cervical lymph nodes after previous total thyroidectomy have had negative ^{75}Selenomethionine scans. One patient had a 1.0 cm. superior deep cervical node replaced by medullary carcinoma with amyloid stroma and the second patient had a 3 cm. cystic papillary adenocarcinoma metastatic to a supraclavicular node.

2. Thyroiditis (Table 3)—four patients with chronic thyroiditis and one patient with granulomatous thyroiditis were evaluated. The patient with granulomatous thyroiditis had unilateral thyroid enlargement, a "cold" scan by radioiodide and a positive scan with ^{75}Selenomethionine. Clinically the findings were in keeping with a malignant tumor of the thyroid. The positive ^{75}Selenomethionine scan was believed to be due to the intense inflammatory cell infiltrate.

Chronic thyroiditis proved to have a characteristic pattern of uptake, namely, a heterogeneous or homogeneous concentration of radioiodide and a uniform uptake of ^{75}Selenomethionine (Fig. 6). The thyroid gland was characteristically diffusely enlarged with configuration of the normal gland maintained.

3. Follicular Adenoma (Table 4)—eight patients with follicular adenomas varying in diameter from two to seven cm. had five positive ^{75}Selenomethionine scans, two that were indeterminate and one that was negative. Those tumors that were large, and highly cellular were associated with positive scans (Fig. 7). The ratio of radio-

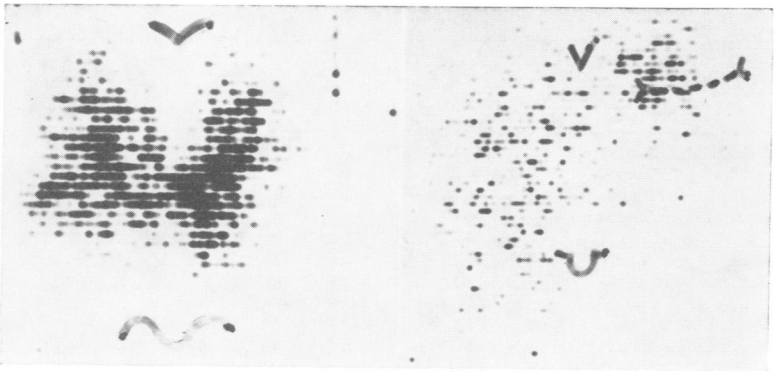

FIG. 2. (a) Radioiodide (left) and ^{75}Selenomethionine scan in a 53-year-old female with undifferentiated tumor involving the upper pole of the left lobe of the thyroid with metastases to cervical lymph nodes. Biopsy site indicated by dotted line on scan.

activity of the tumor to the normal gland at the time of operation was similar to that found in patients with thyroid cancer. The use of the ^{75}Selenomethionine to identify a high cellular adenoma facilitated the differentiation from adenomatous goiter and cysts and discrimination from cancer could only be made by careful histologic study for evidence of blood vessel and/or capsular invasion. One patient with a functioning adenoma had a positive ^{75}Selenomethionine scan.

4. Adenomatous Goiter—twenty-two patients with adenomatous goiter were studied. The nodules varied in diameter from two to seven cm. There were four positive scans and two indeterminate scans. All nodules except three were nonfunctioning when appraised by radioiodide. Of two patients with hyperfunctioning nodules, one was hyperthyroid. The latter had an indeterminate ^{75}Selenomethionine scan which is in keeping with the dirth of cells that is characteristic of many of these hy-

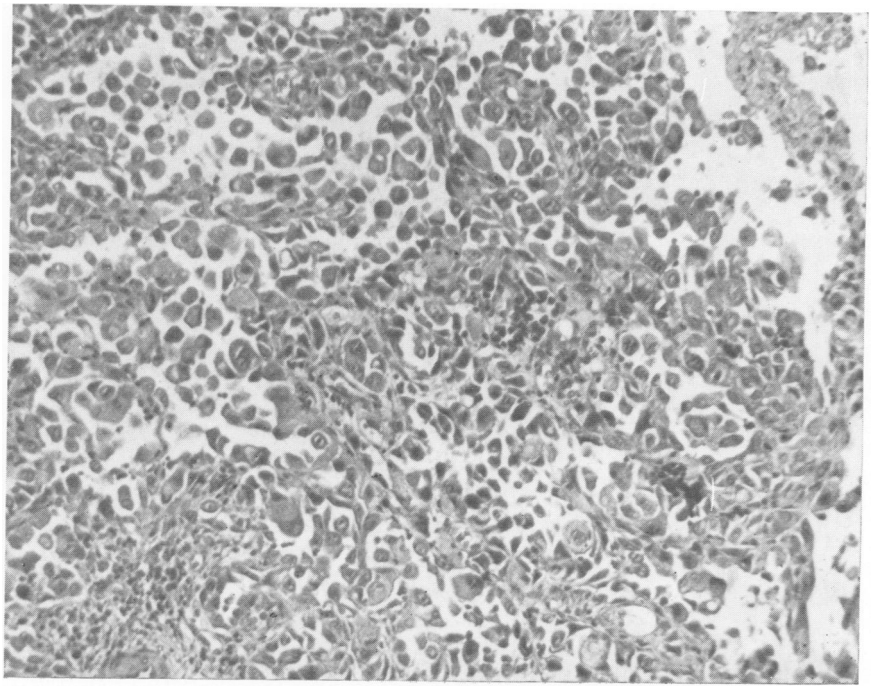

FIG. 2. (b) Photomicrograph. (Hematoxylin and eosin ×130.)

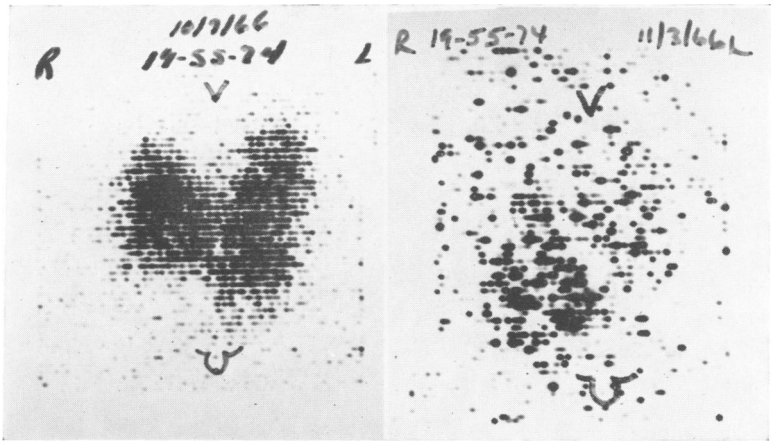

FIG. 3. (a) Complementary photoscans with radioiodine (left) and ^{75}Selenomethionine in a 75-year-old woman with a well differentiated follicular carcinoma involving the right lower pole. The "cold" area in the radioiodide scan is the site of the greatest concentration of the ^{75}Selenomethionine.

perfunctioning nodules. The scan in the other patient was negative. Histologically the adenomatous nodules had a very heterogeneous cellular pattern characterized by acini of varying size, usually with very little cellularity and with most of the acini having low cuboidal epithelium. There were no false negative ^{75}Selenomethionine scans in this group of patients.

Discussion

^{75}Selenomethionine has been used as a tracer to study amino acid and protein metabolism[2]; the uptake of the ^{75}Se-methionine reflecting protein synthesis. The rate of such synthesis and the demand for amino acids will be proportionate to the rate of protein secretion and the rate of protein turnover due in turn to intracellular degradation, resynthesis, and replacement of whole cells. Studies in the experimental animal with partitioning of tissues into cold TCA soluble and insoluble fractions to differentiate incorporation of Selenomethionine into peptide structure of newly formed protein vs. possible binding by a selenosulphur bond to preformed molecules suggest that the amino acid analogue is incorporated into tissue and plasma proteins. Further evidence that this metabolic pathway involves cellular protein synthesis comes from the observation that such incorporation could be partially blocked with puromycin and actinomycin-D.[1]

Free ^{75}Selenomethionine is rapidly cleared from the plasma and by five minutes only 50% of the administered radioactivity remains in circulation. By 30 minutes the ma-

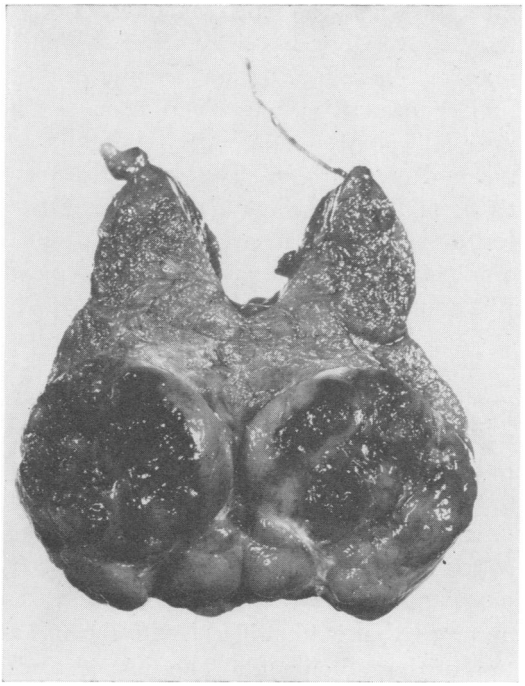

FIG. 3. (b) Gross photo of bisected right lobe.

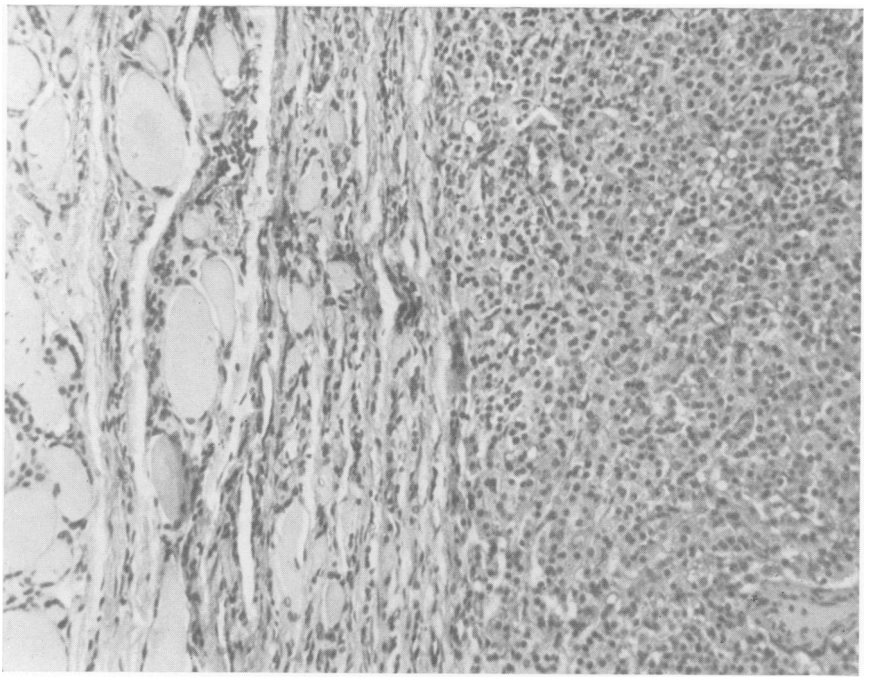

FIG. 3. (c) Photomicrograph comparing the tumor and adjacent normal thyroid. (Hematoxylin and eosin ×130.)

jority of plasma radioactivity is due to that newly incorporated into protein. The greatest uptake is in the pancreas, intestines and liver. The kidney has a high but sustained uptake.[1] These four organs because of their bulk and active metabolism account for over 90% of the total injected isotope at the end of one hour. The low rate of activity in the ovary and bone marrow is a fortunate circumstance in terms of clinical application. The rate of reutilization of ^{75}Selenomethionine is not yet known.[1]

The ability of certain organs or organ systems to concentrate and localize selectively gamma emitting isotopes has permitted appraisal of the dimensions of functional tissue as well as the homogeneity of uptake. In some circumstances a diseased organ will fail to concentrate the isotope as manifest by a "cold" spot. In other circumstances it is the abnormal tissue within an organ that is identified by its concentration of the radionuclide. The thyroid gland is uniquely suitable for such appraisal because of its avidity for iodide. The ability to detect either a "cold lesion" or a "hot lesion" of the thyroid by such scanning technics involves a number of parameters,[6] i.e., absolute count rate, target-nontarget ratio,[3] the resolving capacity of the detector system, the scan speed, the energy of the emitted photon, together with its absorption and scatter properties in the tissues and the visual interpretation of the recorded scan. Of these perhaps that which receives most attention by the clinician is the recorded scan.

Appropriate interpretation of scintigrams requires knowledge of the limitations of the method.[4, 6, 13] Studies involving phantoms have indicated that using the delineation potentials of ^{125}Iodine and ^{131}Iodine lesions are somewhat more readily detected by ^{125}Iodine not only as a surface lesion but also at a depth of 2 cm.[10] Lesions varying in size from 1 to 3 cm. have been readily detected upon the surface. Identification of a cold nodule by scinti-

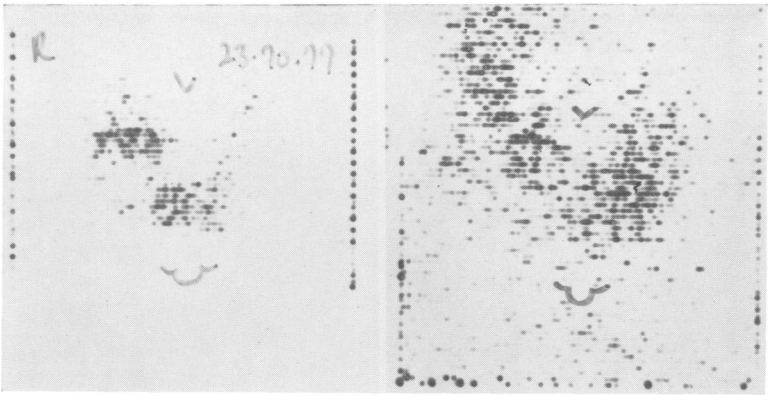

FIG. 4. (a) ^{125}Iodine (left) and ^{75}Selenomethionine scans in an 82-year-old female with a small cell carcinoma of the thyroid with metastases to the lymph nodes of the right neck. The ^{75}Selenomethionine is concentrated at the site of tumor in both lobes as well as in the cervical metastases.

gram is dependent upon displacement or replacement of normal thyroid. The limit of resolution of commercial scanners is 1 cm. and clinical experience has indicated that lesions must be at least 1 cm. in diameter to be identified by scintigram. In nodules of greater size there must be a 20% increase in radioactivity of all thyroid tissue in the same sagittal plane to be detected.

Similar studies with a ^{75}Selenomethionine phantom were carried out in order to determine the size of the tumor that could be detected against a background of radioactivity comparable to that of the neck.[12] A "tumor" of 1 cubic centimeter with an activity of 3 times the background could just be detected. Tumors of 2 cubic centimeters were readily apparent. In the present study the target-nontarget ratio of ra-

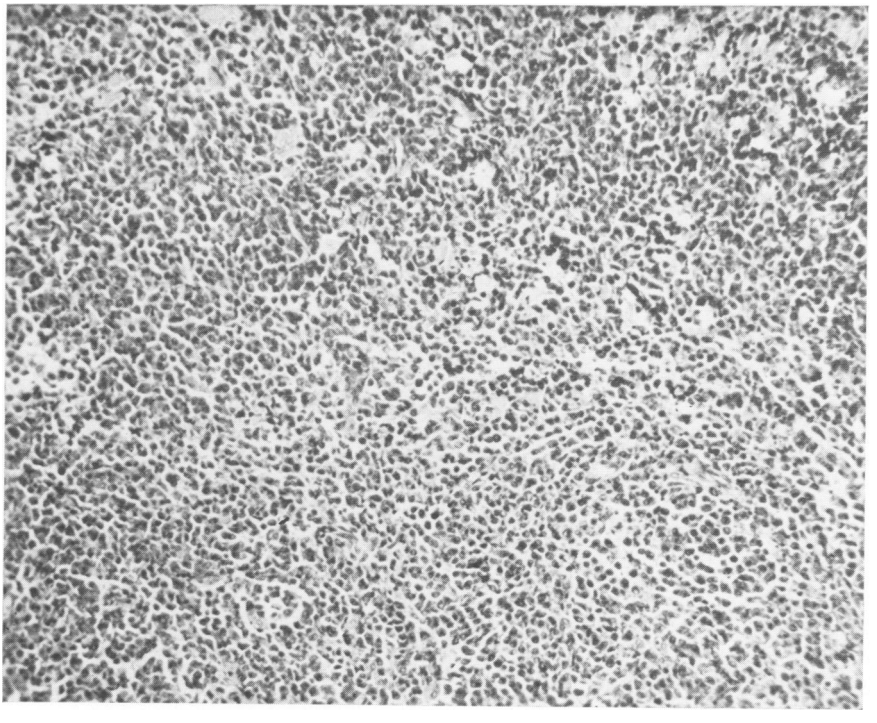

FIG. 4. (b) Photomicrograph. (Hematoxylin and eosin ×130.)

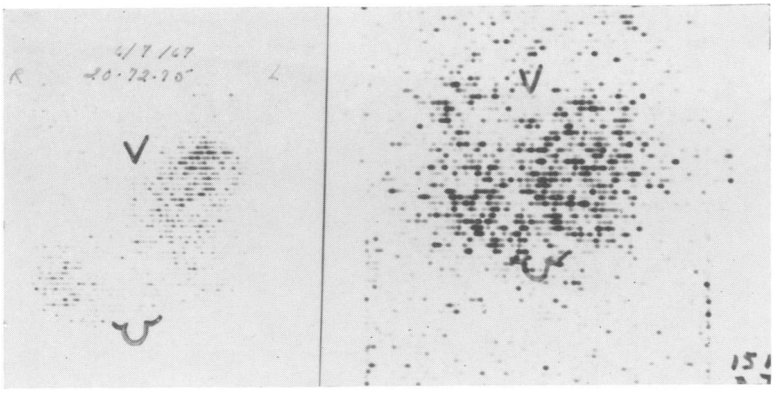

FIG. 5. (a) Photoscans in a 68-year-old female in whom the radioiodide scan (left) disclosed an enlarged left lobe and lack of uptake over isthmus and superior portion of right lobe. A ^{75}Selenomethionine scan (right) discloses uptake throughout the gland.

dioactivity usually varied between two and three. With this low rate of differential uptake it is apparent that the larger the tumor the greater the likelihood of a positive scan. This has also proved to be true of parathyroid adenomas where the differential radioactivity of the adenoma and the thyroid is usually not greater than two or three.[5, 12]

Under these circumstances it is likely that tumors with a diameter of less than 2 cm. will not be identified with ^{75}Selenomethionine by the scanning technics currently available unless the background is further reduced by suppressing thyroid function with exogenous thyroid hormone, e.g., triiodothyronine. When the thyroid is previously blocked by these means the concentration of radioactivity is essentially that of blood.[15] The utilization of subtraction technics may further enhance the specificity of this method.[8]

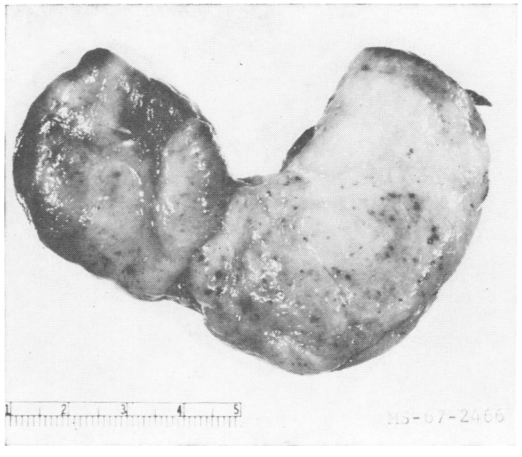

FIG. 5. (b) The gross findings are consistent with malignant lymphoma.

The problem of the nontoxic nodular goiter resolves primarily about its differentiation from thyroid cancer. In view of the frequency of goiter in the adult population which is well documented by autopsy[14] there is a definite need to be selective in the excision of nodules in order to distinguish those due to thyroid cancer.

As in any laboratory examination, the thyroid scintigrams must be used as an adjunct to the overall clinical evaluation and not as the sole criterion of the type of lesion. Such an evaluation takes into consideration the physical findings, the clinical setting in which the nodule occurs, with due regard to the natural history and incidence of both nodular goiter and thyroid cancer. Certainly a nodule in the second or third decade that is not functioning has a much greater likelihood of being malignant than one in the seventh or eighth decade. It is obvious that in the present study considerable selection has already

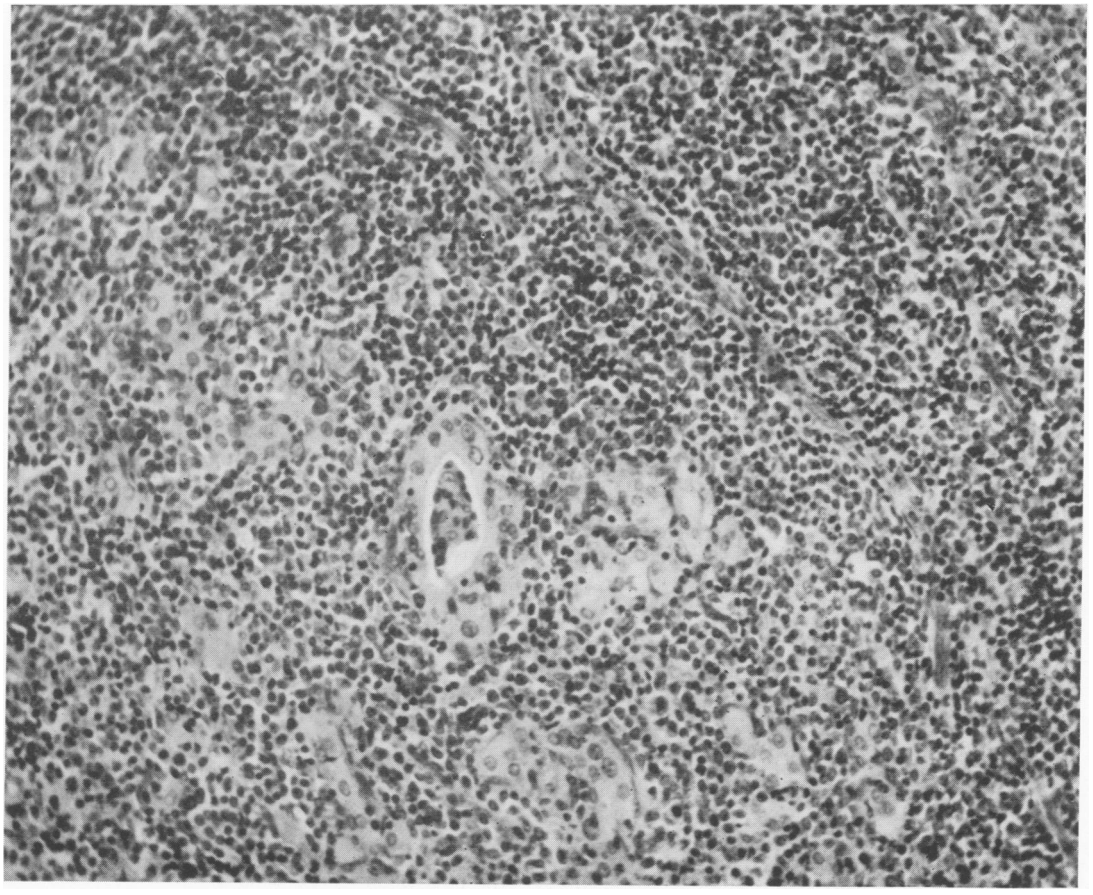

FIG. 5. (c) Histologic findings are characteristic of malignant lymphoma.

TABLE 3. *Uptake of Radioiodine and ^{75}Selenomethionine in Thyroiditis*

Patient	Sex	Age	Diagnosis	Mass in Cm.	^{131}I	^{75}Se	Cell Density	Ratio (tumor:normal) (cpm/mg. wet)
W. W.	M	80	Chronic thyroiditis	4 × 4 × 3	3	4	3	—
N. W.	F	51	Chronic thyroiditis	normal	3	1	3	—
E. M.	F	69	Riedel's thyroiditis	4.5 × 4 × 1	0	4	2–3	—
E. P.	M	63	Granulomatous thyroiditis	3 × 3 × 3	0	1	2	2:1 (24)*
M. S.	F	51	Hashimoto's thyroiditis	Diffusely enlarged	2	3	3	—

* Hours after injection of ^{75}Selenomethionine.

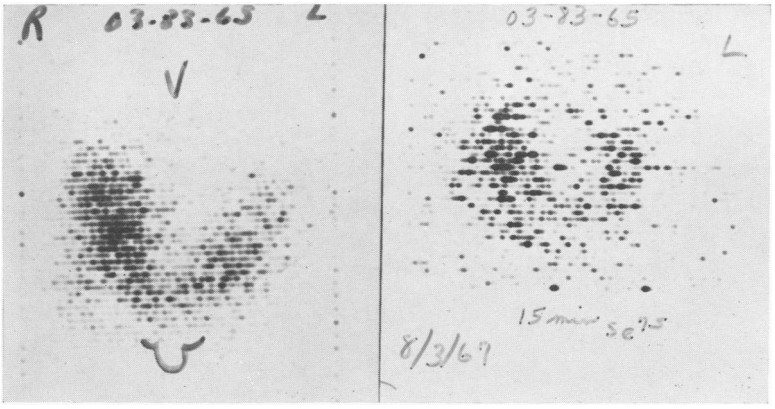

FIG. 6. (a) Photoscans in an 80-year-old male with chronic thyroiditis. Both the radioiodide (left) and ^{75}Selenomethionine discloses a heterogeneous uptake with maintenance of the thyroid configuration.

occurred prior to the evaluation of patients by these methods.

The scanning technics described will positively identify those "tumors" that are cellular with a rapid rate of cell replication. If in the present study of 46 patients only the criterion of a "cold" nodule had been used as an indication for surgery, 38 patients would have been operated upon yielding an incidence of cancer of 29%. If a positive or indeterminate ^{75}Selenomethionine scan was utilized as the only criterion for operation, the incidence of cancer would rise to 38%. However, by the use of complementary scans with both radioiodine and Selenomethionine the incidence of cancer rises to 48%. Thus, one half of the patients would have been spared an unnecessary operation. In none of the patients with cancer would an operation have been omitted. Those patients with false positive scans are individuals with highly

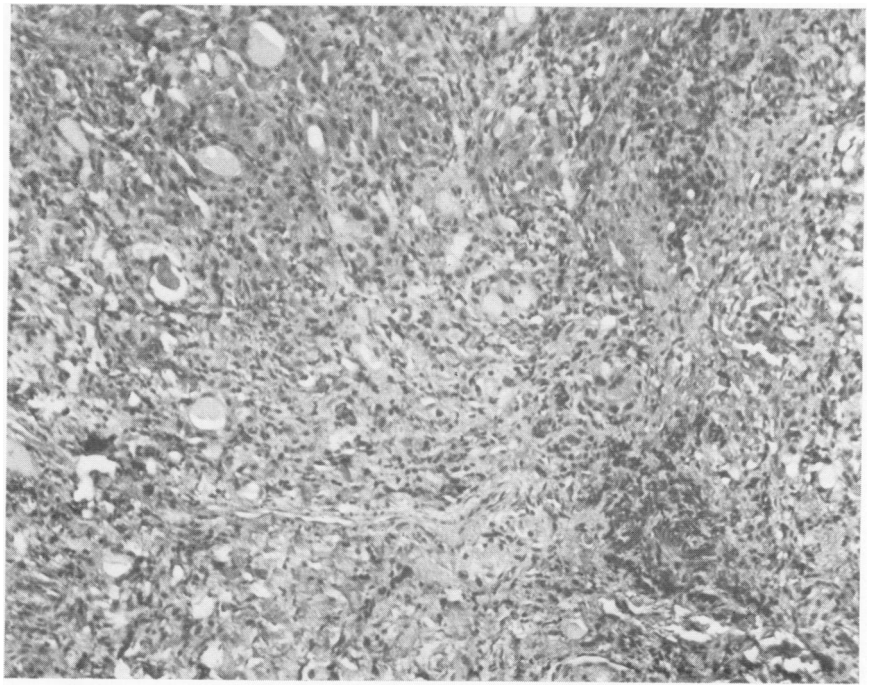

FIG. 6. (b) Photomicrograph. (Hematoxylin and eosin ×130.)

TABLE 4. *Uptake of Radioiodine and ^{75}Selenomethionine in Follicular Adenoma*

Patient	Sex	Age	Diagnosis	Mass in Cm.	^{131}I	^{75}Se	Cell Density	Ratio (tumor normal) (cpm/mg. wet)
D. S.	F	42	Follicular adenoma	4 × 2.5 × 2	1	1	1	—
R. M.	M	61	Follicular adenoma	4 × 4 × 4	0	1	1–3	1.3:1 (1)*
D. B.	M	45	Follicular adenoma	5 × 4.5 × 3	2	0	2	1.3:1 (19)*
J. J.	M	53	Follicular adenoma	3.5 × 3 × 2	0	2	1–3	2.1:1 (44)*
R. M.	F	54	Follicular adenoma	8 × 6.5 × 3	0	4	4	—
H. P.	F	55	Follicular adenoma	4.5 × 4 × 2.5	3	2	2	—
O. W.	M	55	Follicular adenoma (and nodular goiter)	2.5 × 2.5 × 1	0	2	2	2.0:1 (360)*
H. R.	F	45	Follicular adenoma (and ca)	3 × 2.5 × 1.5	0	3	3	—

* Hours after injection of ^{75}Selenomethionine.

cellular or large adenomas or localized thyroiditis in whom a histologic study would be mandatory to identify the lesion.

Summary

Photoscans with radioiodine and ^{75}Selenomethionine were performed in 46 patients in whom thyroid carcinoma was suspect. The uptake of ^{75}Selenomethionine in the thyroid represented the rate of protein synthesis—reflecting mitotic activity and cellularity. The scans proved to be complementary in that a mass "cold" by radioiodide and "hot" with ^{75}Selenomethio-

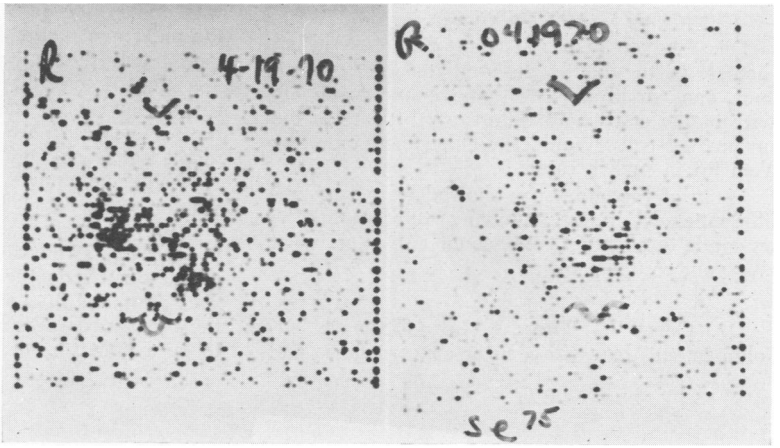

FIG. 7. The ^{75}Selenomethionine scan (left) in this 55-year-old man with a 2.5 cm.^{2} follicular adenoma involving the left lobe was positive. An occult sclerosing 1.5 cm.^{2} adenocarcinoma in the left upper pole was not identified. The radioiodide scan was procured at 6 hours and was regarded as indeterminate because of the low uptake (1.7%).

nine had approximately one chance out of two of being cancer. There were no false negative ^{75}Selenomethionine scans. Utilization of these scanning technics in conjunction with a careful appraisal of the clinical findings permits a more accurate preoperative diagnosis of thyroid cancer and helps eliminate unnecessary surgery for benign lesions of the thyroid.

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Discussion

Dr. Leon Goldman (San Francisco): Dr. Thomas, in the highly differentiated, adenocarcinoma one would suspect that the metabolic activity in the cell would differ very little from the surrounding cells. Would the Selenomethionine be taken up in such a case?

Many of the slides you showed were very undifferentiated, actively growing tumors—in the low-grade tumors that we encounter so often, what have your results shown?

Dr. Colin G. Thomas, Jr. (Closing): Dr. Goldman, this has also been of concern to us and was one reason for limiting the initial study to the older age group. Based upon our studies with a phantom the limitations are those of a tumor less than 1 cm. in diameter. Obviously if the tumor is well differentiated and the cellularity is the same as the normal gland, a mass of this size might not be identified.

In general, however, most of the tumors that we have evaluated had an increased cellularity and even those that were well differentiated had a positive scan. You will observe that there were no negative scans in the patients with cancer.

Thyroiditis in the normal gland will also raise the uptake of ^{75}Selenomethionine and might prove to be a limitation of this method.