USE OF ULTRASOUND AND DIGITAL SCINTIPHOTO ANALYSIS IN THE EVALUATION OF SOLITARY THYROID NODULES

L. G. Thijs, Peter Roos, and Jan D. Wiener

Academisch Ziekenhuis der V.U., Amsterdam, The Netherlands

The introduction of radionuclide scanning (*1*) has permitted the preoperative classification of clinically single thyroid nodules as scintigraphically hyperfunctioning ("hot"), functioning ("warm"), hypofunctioning ("cool"), and nonfunctioning ("cold") (*2*). However, several therapeutic problems have remained unsolved (*3–5*).

Many authors report a high incidence of malignancy in hypo- and nonfunctioning solitary nodules; the figures range from 12.5 to 32% (*2,6–10*) but undoubtedly are influenced by patient selection. A hyperfunctioning nodule, on the other hand, is rarely if ever malignant (*2,6,7,10*). However, the value of the scintigram for the detection of malignancy in the gland is limited (*5,11,12*).

Only *areas* with uneven distribution of radioactivity can be detected on the scintigram. Because the picture is two dimensional, it gives no proof that such an area is a *nodule*. Palpation is generally used for this purpose, but the information added in this way about the "third dimension" of the area is rather inaccurate.

This dimensional problem has been discussed by several authors (*9,13,14*). A hypo- or nonfunctioning nodule may not be delineated on the scintigram. On the other hand, many nodules are not recognized by palpation as has been shown in a postmortem study (*15*). In addition, not all hypofunctioning areas are nodules, some being due to fibrosis, focal thyroiditis, etc. Descriptive terminology has therefore given rise to considerable confusion (*16*).

Recently ultrasound was introduced as a diagnostic tool in the field of clinical thyroid investigation (*17–20*). Aside from the fact that this technique may provide information on structures within the gland such as cystic degeneration (*18–20*), it offers data on the presence of the gland or of a lobe (*19,20*) as well as on the size of the gland as a whole or of a nodule in the transverse plane at a chosen level. In 16 patients who came to operation, estimations of the size of lobes or nodules from the ultrasonic tomogram were compared with measurements of the excised tissue; the difference was less than 5 mm in all the patients, and less than 2 mm in 12 of them (*20*).

The basic principle behind this method is the partial reflection of ultrasound at tissue boundaries or interfaces which have a specific acoustic impedance mismatch (*21,22*). The two-dimensional display technique produces a cross section at the level examined, the places of reflection being represented as dots on an oscilloscope screen; the resulting photographic representation is called an ultrasonic tomogram or B-scan (*22,23*). It has been shown (*17, 18,20*) that the normal thyroid appears on the ultrasonic tomogram, at least at low probe sensitivity, as an echo-free zone between the adjacent structures which elicit strong echoes. In this way the size of the gland can be measured in a transverse plane and the position, width, and depth of nodules can be established and correlated to the scintigraphic data.

The introduction of Anger's gamma camera (*24*) brought about a fundamental change in the radioactive scanning technique. Addition of a memory matrix (multichannel analyzer or computer system) to the camera introduced the possibility of a permanent record of digital events.

We have studied a series of patients with clinically solitary thyroid nodules by means of (analog) scintiphotography, digital scintophoto analysis, and ultrasonic tomography with the aim of improving the detection of hypo- and nonfunctioning nodules.

MATERIALS AND METHODS

One hundred and two patients with clinically solitary thyroid nodules were included in the study. They were referred to the Institute for the evaluation of

Received May 10, 1971; revision accepted Feb. 10, 1972.

For reprints contact: L. G. Thijs, Dept. of Internal Medicine, Academisch Ziekenhuis der V.U., 1117 de Boelelaan, Amsterdam 1011, The Netherlands.

thyroid function, most commonly because of thyrotoxic signs or the presence of a nodule. The study included 3- and 24-hr ^{131}I uptake, absolute iodine uptake, 3-hr conversion ratio (*25*), and 24-hr serum hormonal radioiodine (*26*). Furthermore, serum hormonal iodine (HI) (*27*) and T_3 resin uptake (RU) were determined, and the free thyroxine index (FTI $= HI \times RU$) was calculated. In four patients a T_3 suppression test was carried out.

Scintiphotos were made 1 hr after an oral dose of $^{99m}TcO_4^-$ with a gamma camera (Pho/Gamma III, pinhole collimator, 20% window, 50-K preset counts) on Polaroid and x-ray film. The position of the nodule was marked on the skin with ballpoint during palpation preceding scintiphotography. Small 10-μCi ^{57}Co marker sources were attached on the skin at the site of thyroid cartilage and sternal notch, and the distance between these sources was measured. The patient was seated in a chair with the head slightly hyperextended. The analog x-, y-, and counting-rate signals were stored after ADC conversion in the 64×64 memory matrix (Nuclear-Chicago 4,096 analyzer) and recorded on Polaroid film after data smoothing. Display was usually in the gray scale mode, sometimes with lower level control to enhance contrast.

A second scintiphoto was made with a marker source at the site of the nodule. A transverse profile display through the nodule was photographed on Polaroid film using the first recording (without markers) with the display controls readjusted.

Ultrasonic investigations were carried out with the Diasonograph (Nuclear Enterprises, Type NE 4101) by kind permission of Prof. Janssens, Department of Obstetrics and Gynecology. Optimal contact between probe and neck was achieved with a thin layer of Brylcreem® on the skin. The patient was seated in the same position as during scintiphotography. The ultrasonic 2.5-Mc probe, which serves both as transmitter and receiver, was gently moved horizontally over the thyroid region at the level where the radioactive profile had been made, making short rocking movements without losing skin contact. In order to obtain optimal echo information, the sector scanning system was modified as described by Donald (*23*). Sensitivity was set at a "low" value because in these studies we were only interested in the outlines of the gland or the nodule. The results were recorded from the oscilloscope screen on Polaroid film using time exposure photography. With increasing sensitivity the thyroid shows finely dispersed echos and is gradually "filled up". Because there are individual variations, "low sensitivity" was arbitrarily defined as the level at which the gland is completely echo-free while the surrounding structures give clear echos.

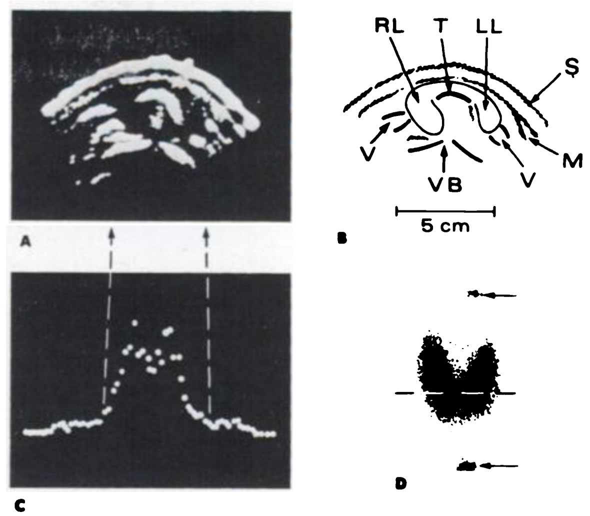

FIG. 1. Normal thyroid gland. A shows ultrasonic tomogram at level indicated on scintigram (D). B is schematic representation of A. T is anterior wall of trachea; RL, right lobe; LL, left lobe; V, vascular sheath; S, skin and probe artifact; VB, vertebral body; M, sternomastoid muscle. C shows radioactive profile at same level as A. Arrows indicate lateral borders of lobes. D is scintiphoto. Arrows indicate marker sources on thyroid cartilage and sternal notch.

RESULTS

The ultrasonic tomogram, the scintiphoto, and the transverse profile at the indicated level of a completely normal thyroid is shown in Fig. 1 for reference.

Table 1 summarizes the results in the patients. Nodules delineated on the scintiphoto by size alone (scintigraphically "warm") and those which are not delineated at all, placed into separate categories by Miller, Hamburger, and Mellinger (*13*), were considered not to be fundamentally different and have therefore been taken together in one group (isoactive or "warm").

Fifty-three patients, all of them euthyroid, showed a "cool" or "cold" area on the scintiphoto corresponding to the nodule. In 26 patients the nodule was situated in the right lobe, in 18 in the left lobe, and in 9 in the isthmus. In most cases some activity, usually irregularly distributed, was present in the nodule. The ultrasonic tomogram clearly showed the outline of the nodule in almost all patients (Fig. 2). After calibration the size of the nodule could be measured in the transverse plane, providing an objective measure of the depth and width of the nodule and confirming that the area of diminished activity on the scintiphoto was indeed a nodule.

Thirty-three patients presented a single relatively hyperfunctioning area corresponding to the palpated nodule, which was situated in the right lobe in 17,

TABLE 1. FUNCTIONAL CLASSIFICATION OF NODULES

Classification of nodule from scintiphoto	Total No.	Final clinical diagnosis		Classification of nodule from scintiphoto and ultrasonic tomogram together	
		Hyperthyroid	Euthyroid	Hyper-functioning	Hypo- or non-functioning
Hypofunctioning ("cool" and "cold")	53	—	53	—	53
Hyperfunctioning ("hot")	33	19	14	33	—
Functioning (isoactive, "warm")	13	—	13	—	13
Presumably "cold"*	3	—	3	—	3

* Classification was impossible from the scintiphoto alone, because no relatively hyper- or hypo-functioning areas were visible. A slight indentation at the lateral border of a lobe corresponding with a palpable nodule suggested the presence of a cold nodule situated outside of the gland.

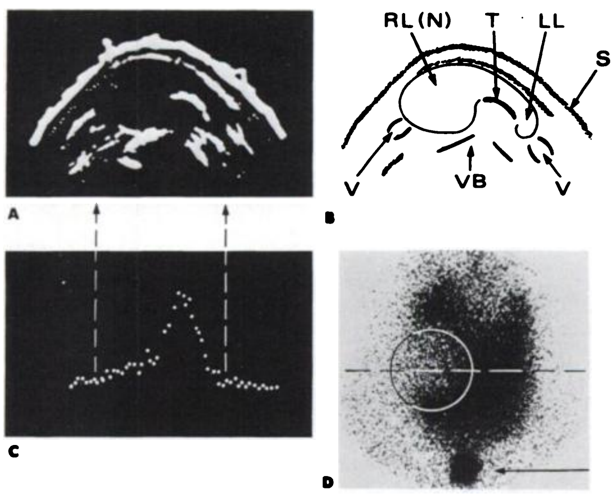

FIG. 2. Euthyroid patient with hypofunctioning nodule in right lobe. A shows ultrasonic tomogram. B is schematic representation of A. Nodule, N, in the right lobe is clearly visible. C, radioactive profile at same level shows most of nodule to be hypofunctioning whereas enlarged isthmus is relatively hyperfunctioning. D is scintiphoto showing hypofunctioning area in right lobe and broadened and relatively hyperfunctioning isthmus. Circle indicates site where nodule was palpated.

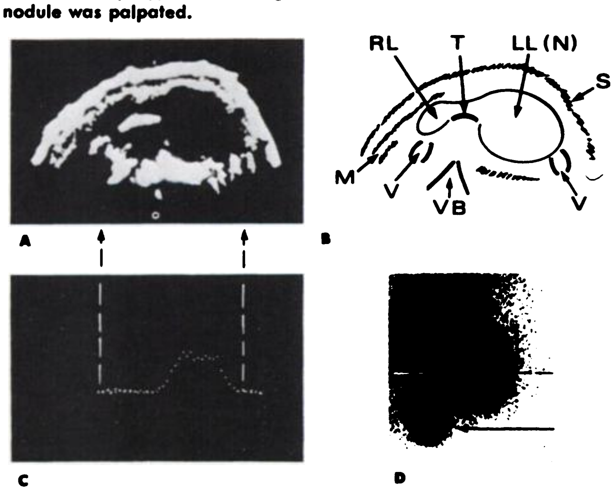

FIG. 3. Patient with toxic nodule. A shows ultrasonic tomogram. B is schematic representation of A. Left lobe is completely replaced by nodule. Right lobe, not visible on scintiphoto, D, is clearly delineated on ultrasonic tomogram. C is radioactive profile at same level. Activity in nodule is regularly distributed. D is scintiphoto. All activity is contained in nodule.

in the left lobe in 10, and in the isthmus in 6 patients. In 4 of the 14 euthyroid patients the nodule was shown to be functionally autonomous by means of a T_3 suppression test; in the other 10 this test unfortunately could not be carried out. Normal thyroid tissue was completely suppressed in 16 of the 33 patients. In most patients the distribution of radioactivity within the nodule as documented on the scintiphoto and the transverse profile was essentially homogeneous. In a few patients, however, irregularities could be seen within the nodule, suggesting the presence of degenerative processes. With the ultrasonic tomogram the distribution of the radioactivity could be objectively related to the depth and width of the nodule. Furthermore, when the hyperfunctioning nodule completely suppressed the perinodular tissue, the ultrasonic tomogram showed the presence and the size of the other lobe (Fig. 3).

Thirteen patients form a particularly interesting group. A solitary nodule was palpable but delineated on the scintiphoto either by size only (eight patients) or not at all and would therefore be classified as "warm" on the basis of the scintiphoto alone. The ultrasonic tomogram showed, however, that these nodules were thicker than the surrounding tissue and therefore hypofunctioning per unit volume (Figs. 4 and 5). Actually, they might even be "cold", the "warm" appearance on the scintiphoto being caused by overlying normal thyroid tissue (see discussion).

When, on the other hand, a nodule is normally active per unit volume, it will appear as relatively hyperactive on the scintigram if it is thicker than the surrounding tissue. An example (not included in Table 1) is shown in Fig. 6.

In the remaining three patients of this series a slight indentation formed the only scintigraphic clue to the presence of a nodule. The ultrasonic tomogram clearly showed the presence of a nodule situated almost entirely outside the gland. A combination of palpatory, scintigraphic, and ultrasound data al-

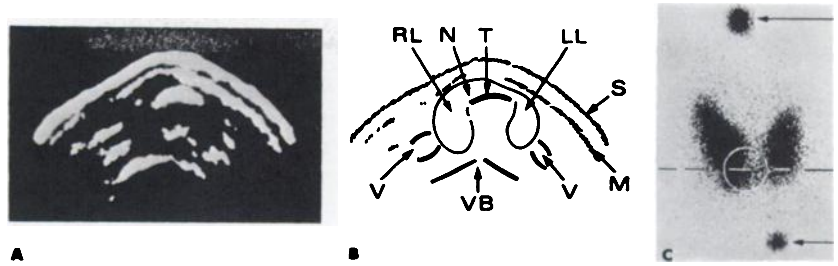

FIG. 4. Euthyroid patient with small nodule in isthmus. A shows ultrasonic tomogram. B is schematic representation of A. Nodule is clearly delineated at right lateral part of isthmus. In C scintiphoto is grossly normal, but palpable nodule (circle) is not delineated. From inference, however, nodule has to be classified as hypo- or nonfunctioning.

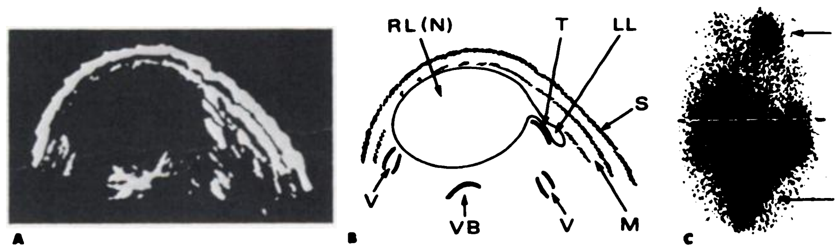

FIG. 5. Euthyroid patient with enlarged right lobe clinically palpable as very large nodule. A shows ultrasonic tomogram. B is schematic representation of A. Right lobe is completely replaced by nodule. C is scintiphoto. Nodule seems to be essentially isoactive ("warm"). Yet when scintiphoto is related to ultrasonic tomogram, it is clear that nodule is markedly hypofunctioning per unit volume.

lowed the classification of these cases as nonfunctioning nodules.

Comparison of the scintigraphic data with the ultrasonic tomogram further showed the size of hypofunctioning and hyperfunctioning nodules to be under- and overestimated, respectively, by 2–5 mm on the scintiphoto. This is in accordance with the distorting effect of the pinhole collimator used for scintiphotography. As mentioned earlier, the ultrasonic tomogram accurately reflects the true size.

DISCUSSION

The results presented here show that the use of diagnostic ultrasound offers the possibility of visualizing and measuring the size of the thyroid gland or of a nodule in a transverse section at any level of the neck. In an earlier study (*20*) it has been shown that at high sensitivity this technique can distinguish between a solid thyroid tumor and a cystic lesion; in patients with a hypo- or nonfunctioning nodule this information is of great value because a simple cyst is less suspicious for malignancy (*8*). Also, cystic degeneration within a solid structure can be detected. Finally, the ultrasonic technique should be a valuable additional tool in the followup of patients who are either left untreated or are treated with ^{131}I or thyroid hormone.

The technique is of particular importance in patients with a palpable or suspected nodule which is delineated on the scintiphoto by size alone or not

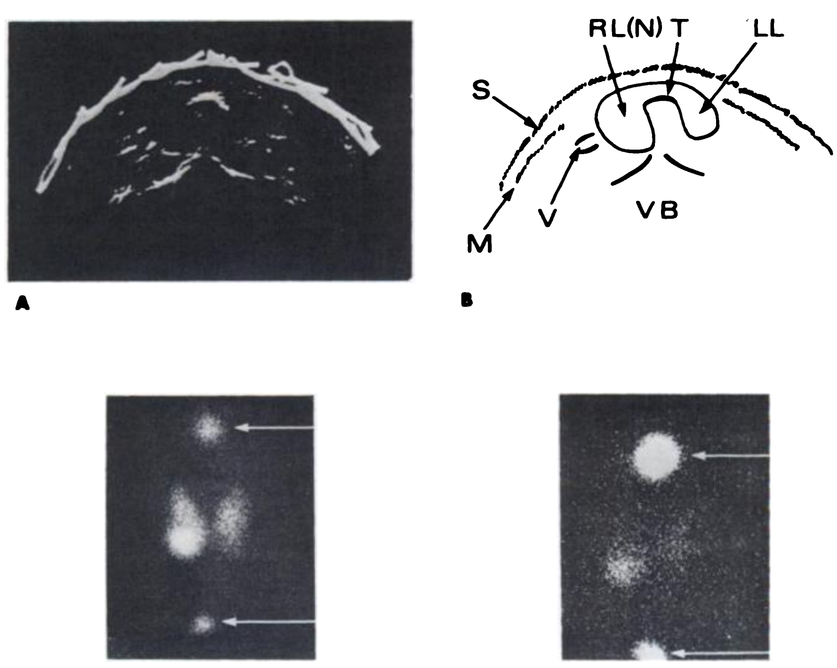

FIG. 6. Euthyroid patient with scintigraphically hyperactive nodule in right lobe. A shows ultrasonic tomogram at level of nodule. B is schematic representation of A. Depth of right lobe (nodule) is approximately 1½ times that of left lobe. C is scintiphoto showing relatively hyperactive nodule in right lobe. Digital readout with multichannel analyzer showed nodule to contain 37% of entire thyroid radioactivity or 1.2 times activity contained in left lobe. D is scintiphoto made during T_3 suppression. Both nodular and perinodular activity are suppressed, demonstrating that nodule is not functionally autonomous. When ultrasound and scintigraphic data are combined, nodule appears to be approximately normally active per unit volume.

at all as was the case in 13 of our patients. The presence of these nodules and their hypo- or nonfunctional state could be ascertained in an objective and measurable way. This is of clinical importance because hypo- and nonfunctioning nodules are often malignant. The activity seen on the scintigram at the site of the nodule in these cases either stems from normal tissue overlying the nodule or is contained in the nodule itself. In the latter case the misleading scintigraphic picture is caused by the greater depth of the nodule in comparison with the perinodular tissue, the activity in the nodule being normal ("warm") per unit surface but low per unit volume. Some of the nodules, particularly of the first category, are cysts, and these can be diagnosed by ultrasonic tomography at high sensitivity (*19,20*). The combination of ultrasonic tomogram, scintigram, and radioactive profile makes it possible to estimate the activity per unit volume from the activity per unit surface.

By analogy, the ultrasonic tomogram may show a local increase of radioactivity (per unit surface) on the scintigram to be due to increased depth of the glandular tissue at that site, the activity per unit volume being similar to that of the perinodular tissue. In that case, the scintigraphically "hot" nodule should actually be considered as "warm". A simple ultrasound study may obviate the need for a T_3 suppression test in these patients.

Our experience with digital scintiphoto analysis providing image displays and radioactive profiles at the same level as the ultrasonic tomogram demonstrates that this tool is of additional help in estimating the radioactive distribution within a nodule. However, one has to realize that the total number of counts in one profile line is statistically rather low; therefore random variation may have a distorting influence. "Smoothing" of the original image will take away at least part of this influence but will slightly diminish the resolution. Moreover, radioactivity coming from deeper parts of the gland has relatively less influence on the counting rate because of tissue absorption. The distance response of the detector will not have much influence because the neck-crystal distance is large in comparison with the thickness of the thyroid.

A few limitations of the ultrasonic technique should be mentioned. In some patients it was not possible to outline clearly the lateral border of the thyroid or of the nodule. We presume this is inherent to the method itself because the ultrasonic beam is best reflected when the object is hit perpendicularly, which in the complex anatomy of the neck will not always be the case. Another drawback is the fact that the ultrasonic tomogram is usually made at one level only. Making tomograms at several levels of the neck is time-consuming, one picture taking 15 min to complete. Yet in selected patients it may be fruitful to do so in order to get a better insight into the anatomical relationships.

Our experience with diagnostic ultrasound and digital scintiphoto analysis warrants further investigation in patients with thyroid pathology. The combination of palpation, digital scintiphotography, and ultrasonic tomography may lead to a better classification of thyroid nodules and a better appreciation of the value of scintigraphy in the pathology of thyroid nodules.

SUMMARY

Thyroid scintigraphy is widely accepted as the only means to study thyroid nodules detected by palpation. Accordingly these nodules are classified as "hot", "warm", "cool", or "cold". Cool and cold nodules are often malignant, hot nodules nearly always benign. In this paper digital scintiphoto analysis with a multichannel system is combined with ultrasonic tomography, which adds a third dimension (depth) to the two-dimensional scintigraphic picture. In this way nodules can be shown to be hypo- or nonfunctioning which appear as warm areas on the scintiphoto. This proved to be the case in 13 of 102 patients with clinically single thyroid nodules. Similarly, an increase in radioactivity per unit surface (hot area) may prove to be due to a local thickening of normally functioning thyroid tissue. The addition of ultrasonic tomography as a diagnostic tool may thus help avoid misclassification of thyroid nodules which is not uncommon if performed on the basis of palpation and scintigraphy alone.

ACKNOWLEDGMENT

The skillful and enthusiastic help of W. Stroes is gratefully acknowledged.

REFERENCES

1. CASSEN B, CURTIS L, REED C, et al: Instrumentation for ^{131}I use in medical studies. *Nucleonics* 9: No 8, 46–50, 1951

2. MEADOWS PM: Scintillation scanning in the management of the clinically single thyroid nodule. *JAMA* 177: 229–234, 1961

3. PERLMUTTER M, SLATER SL: Which nodular goiters should be removed? *New Eng J Med* 255: 65–71, 1956

4. SOKAL JE: The problem of malignancy in nodular goiter—recapitulation and a challenge. *JAMA* 170: 405–412, 1959

5. KENDALL LW, CONDON RE: Prediction of malignancy in solitary thyroid nodules. *Lancet* i: 1071–1073, 1969

6. GROESBECK HP: Evaluation of routine scintiscanning of nontoxic thyroid nodules. I. The preoperative diagnosis of thyroid carcinoma. *Cancer* 12: 1–5, 1959

7. PERLMUTTER M, SLATER SL, ATTIE J: Method for preoperative differentiation between the benign and the possibly malignant solitary nontoxic thyroid nodule. *J Clin Endocr* 14: 672–673, 1954

8. MELLIERE D, MASSIN JP, CALMETTES C, et al: Le risque de malignité des nodules froids thyroïdiens. *Presse Med* 78: 311–314, 1970

9. TAYLOR S, PSARRAS A: The solitary thyroid nodule—benign or malignant. *Praxis* 56: 370–374, 1967

10. JACKSON IMD, THOMSON JA: The relationship of carcinoma to the single thyroid nodule. *Brit J Surg* 54: 1007–1009, 1967

11. KENDALL LW, CONDON RE: Radioiodine scans in the diagnosis of the thyroid. *Rev Surg (Phila)* 27: 57–58, 1970

12. SHIMAOKA K, SOKAL JE: Differentiation of benign and malignant thyroid nodules by scintiscan. *Arch Intern Med (Chicago)* 114: 36–39, 1964

13. MILLER JM, HAMBURGER JI, MELLINGER RC: The thyroid scintigram. II. The cold nodule. *Radiology* 85: 702–710, 1965

14. MCCREADY VR: Radioisotopes in the diagnosis of thyroid carcinoma. In *Tumours of the Thyroid Gland*, Smithers D, ed, Edinburgh and London, E and S Livingstone, 1970, pp 202–217

15. MORTENSEN JD, WOOLNER LB, BENNETT WA: Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocr* 15: 1270–1280, 1955

16. WIENER JD: Toxicity, nodularity, activity, autonomy —"coming to terms" in thyroid investigation. *J Nucl Med*: 12: 318, 1971

17. FUJIMOTO Y, OKA A, OMOTO R, et al: Ultrasound scanning of the thyroid gland as a new diagnostic approach. *Ultrasonics* 5: 177–180, 1967

18. RASMUSSEN SN, CHRISTIANSEN NJB, JORGENSEN JS, et al: Differentiation between cystic and solid thyroid nodules by ultrasonic examination. *Acta Chir Scand* 137: 331–333, 1971

19. ROBERT J, LECLERE J, BERTRAND A, et al: Apport des ultra-sons au diagnostic des affections thyroïdiennes. *Ann Endocr (Paris)* 32: 114–123, 1971

20. THIJS LG: Diagnostic ultrasound in clinical thyroid investigation. *J Clin Endocr* 32: 709–716, 1971

21. GORDON D: *Ultrasound as a Diagnostic and Surgical Tool.* Edinburgh and London, E and S Livingstone Ltd, 1964

22. WELLS PNT: The present status of medical ultrasonic diagnostics. *Biomed Engin* 5: 378–385, 1970

23. DONALD T: Ultrasonics in obstetrics. *Brit Med Bull*: 24, 71–75, 1968

24. ANGER HO: *Rev Sci Instrum* 27, 29, 1958 (cited in Anger HO: The scintillation camera for radioisotope localization. In *Radioisotope in der Lokalisationsdiagnostik*, Stuttgart, F. K. Schattauer Verlag, 1967, pp 1–21)

25. WIENER JD: The three-hour conversion ratio: a test for hyperthyroidism. *Acta Endocr (Kobenhavn)* 61: 151–163, 1969

26. WIENER JD, ROOS P: Determination of hormonal radioiodine in serum with a cation exchange resin. *J Nucl Med* 9: 601–603, 1968

27. BACKER ET, POSTMES THJ, WIENER JD: Determination of thyroid homones in serum by means of a cation exchange resin and chloric acid digestion. *Clin Chim Acta* 15: 77–85, 1967