SINGLE THYROID NODULES*

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Single thyroid nodules deserve to be treated as a separate clinical entity for 2 reasons. Firstly, about 20% of them are malignant,[1, 2] and secondly, less than the routine resection of thyroid tissue need be performed for hyperfunctioning nodules.[3]

These nodules are classified as *single* entirely on the basis of the clinical examination and while this has obvious shortcomings, it stresses the importance of a careful assessment of the gland. They are therefore more correctly termed *clinically single nodules.*

On histological examination they are of two main types:

1. A dominant nodule in a multinodular goitre.
2. Neoplastic.

The pathological process accounting for this clinical dominance in type 1 may be one of four:

(*a*) Cystic degeneration

(*b*) Haemorrhage

(*c*) A hyperfunctioning nodule, or

(*d*) Non-benign change in a multinodular gland.

The neoplastic group (type 2) includes:

(*a*) The benign adenomas of various histological patterns, and

(*b*) carcinoma which is usually of the more differentiated variety if the clinical presentation has been that of a single nodule.

The patient with a single thyroid nodule will present to the doctor in one of the following ways: The lump may be entirely asymptomatic and found only on a routine examination of the neck. Secondly, there may be a sudden painful enlargement which usually denotes haemorrhage. Thirdly, there may be pressure symptoms, but this is less common in single nodules; and finally a hyperfunctioning nodule may present with clinically evident toxicity.

If physical examination of a patient in any of these categories reveals a clinically single thyroid nodule, then one of two courses may be adopted. Firstly the nodule can be treated surgically in all cases, with only a prior investigation of possible toxicity for the purpose of its pre-operative control. If this method is followed, the diagnosis will primarily be left to the histologist. Or, secondly, an attempt may be made at a more accurate assessment of the nodule, particularly in regard to its functional capacity for taking up iodine. The diagnostic procedure of choice for this purpose is a scintigram. The technique used records quantitatively the uptake of iodine by various parts of the gland, following an administration of a tracer dose of ^{131}I ($\pm$ 50 μc.). A pattern of the relative function of areas of the gland can thus be obtained. The uniform function of the normal gland presents the appearance seen in Fig. 1.

If this investigation is applied to single nodules, they can be classified on the basis of the resultant pattern into: (1) functioning, and (2) hypo-functioning nodules.

The functioning group may be further subdivided into

(*i*) *hyperfunctioning*, in which the iodine has either been taken up exclusively by the nodule or to a greater degree than the rest of the gland, which is then totally or partially suppressed, and

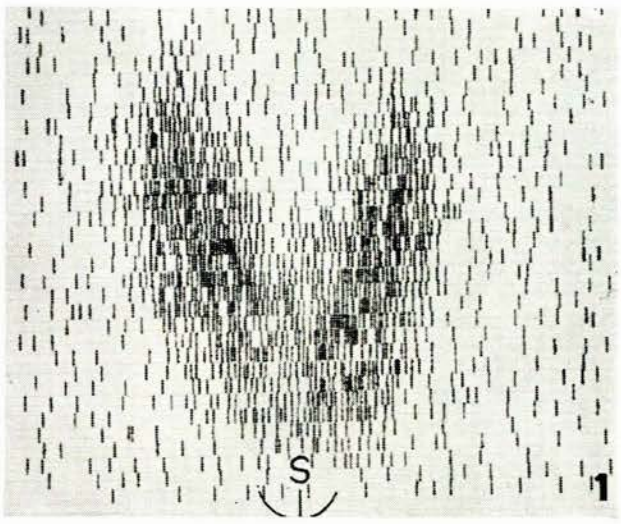


Fig. 1. Scintigram of the normal thyroid gland showing its relatively uniform function. S=sternal notch.

(*ii*) *functioning nodules*, with an equivalent uptake to the remainder of the gland.

The hypo-functioning group includes both

(*i*) *the completely non-functioning nodule* and also

(*ii*) *the hypo-functioning*, with some uptake but less than the remainder of the gland.

The terms 'hot' and 'warm' nodules are sometimes applied to the functioning group, and 'cool' and 'cold' to the hypo-functioning group.

We thus have 4 types of single nodule on the basis of the scintigram giving the classification:

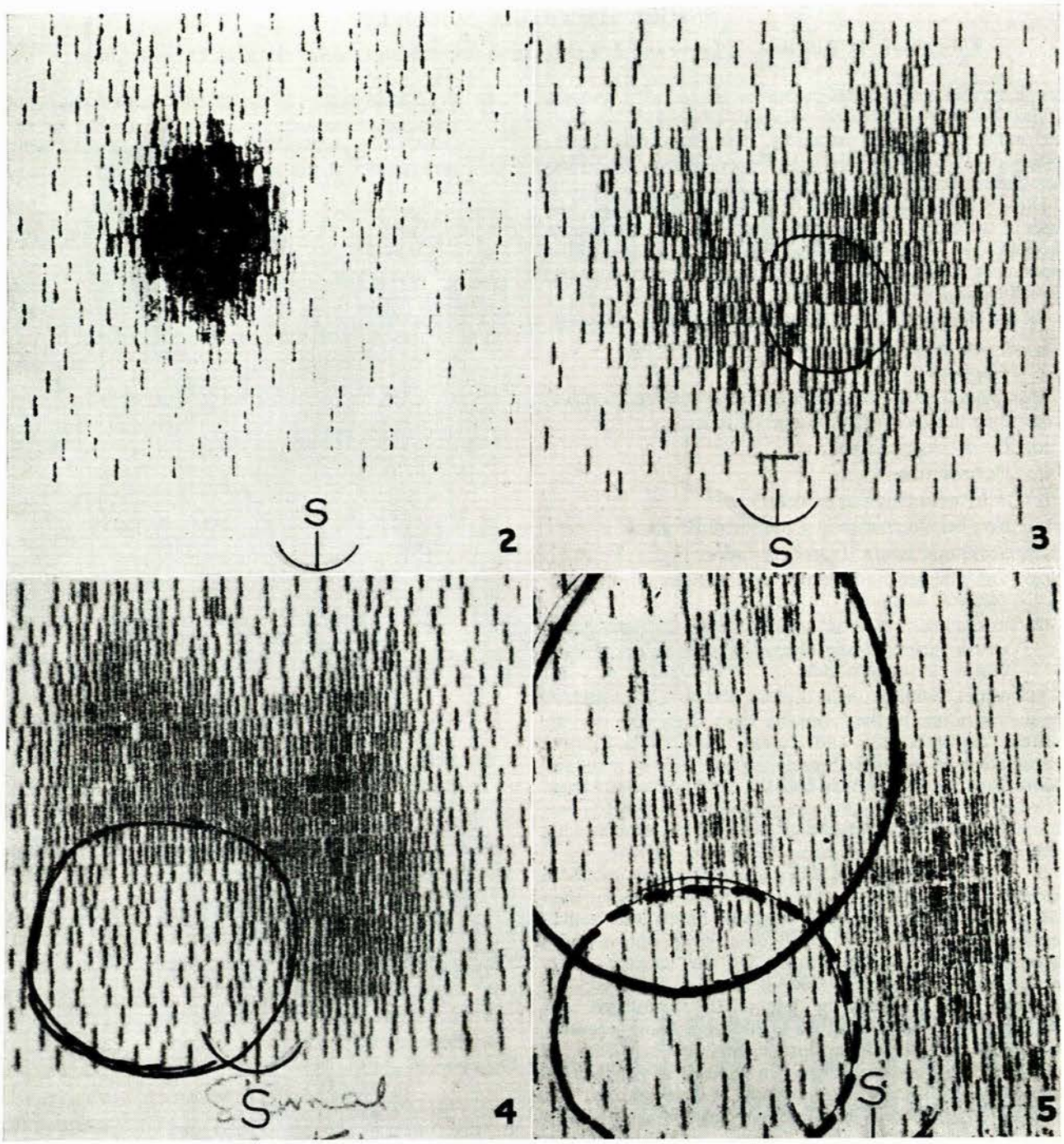
1. Hyperfunctioning or 'hot' nodule.
2. Functioning or 'warm' nodule.
3. Non-functioning or 'cold' nodule.
4. Hypofunctioning or 'cool' nodule.

Examples of each type are shown in Figs. 2 - 5.

HYPOFUNCTIONING GROUP

It was stated at the outset that the importance of the clinical recognition of the single nodule lay in the fact that it might be malignant. On the basis of the scintigram neoplastic nodules are non-functioning, since they are always less avid for iodine than normal gland tissue. For technical reasons this rule cannot be applied absolutely because a small tumour could be masked by overlying functioning gland and the scan is not performed at different cuts or horizontal planes of the gland. However, it operates in almost 100% of cases and in our experience at the Johannesburg General Hospital Thyroid Clinic no functioning single nodule has subsequently proved to be

*Paper presented at the 44th South African Medical Congress (M.A.S.A.), Johannesburg, July 1963.



Figs. 2 - 5. Four types of thyroid nodules can be differentiated on the basis of scintigrams: *Fig. 2.* Hyperfunctioning nodule; *Fig. 3.* Functioning nodule; *Fig. 4.* Non-functioning nodule; and *Fig. 5.* Hypofunctioning nodule. S=sternal notch.

neoplastic. In the analysis of our figures 75% of the hypofunctioning nodules are benign, being either areas of cystic degeneration or haemorrhage in a multinodular goitre or else true benign neoplasms. Table I shows the results of an analysis of our local experience at the Thyroid Clinic and compares this with some of the published figures from other clinics.

At present there is no reliable, further, diagnostic procedure in general use for separating the neoplasms from the remainder of the hypofunctioning group without surgery. There is some prospect of this being possible in the reports by Ackerman and Marvin,[8] using radioactive

phosphorus. Actively mitosing tissue has a higher turn-over of phosphorus and thus, if a tracer of $^{32}P(\frac{1}{2}\ \mu c.)$ is given, a higher count will be obtained over a mitotic lesion when compared with the remainder of the gland. Ackerman and

TABLE I. INCIDENCE OF MALIGNANCY IN THYROID NODULES

	Total number	*Neoplastic*		*Hyperplastic (adenomatous colloid)*
		Carcinoma	*Adenoma*	
Non-functioning (cold)	23	9—39%	9—39%	5—22%
Meadows[4]	24	14—58%		
Hypo-functioning (cool)	17	1—6%	1—6%	15—88%
Meadows	43	2—5%		
Hypo-functioning as a Total:				
Group ..	40	10—25%	10—25%	20—50%
Meadows ..	67	16—24%		
Johnson[5] ..	32	10—31%		
Perlmutter[6] ..	99	23—23%		
Greene[7] ..	109	22—20%		

colleagues[9] have modified this technique using X-ray film applied to the neck to obtain a pattern of radioactivity over the tumour.

In our experience needle biopsy has not proved reliable either. For these reasons our present policy is to recommend *surgical removal for all hypofunctioning single nodules*.

If facilities for frozen section are available they should be utilized in the operative approach to these nodules. If not, then the definitive procedure will either be decided on the macroscopic appearance of the nodule or else be delayed until histological confirmation is available.

(a) If the lesion is a dominant nodule in a multinodular gland, then a partial resection, tailored to the individual case, would be performed.

(b) If it is a benign adenoma, a sub-total or total lobectomy with removal of the isthmus is advised.

(c) If the lesion is malignant, a 'modified' total thyroidectomy is performed. A small posterior slice of gland is left behind on one side or bilaterally, if the situation of the tumour permits this. Leaving this remnant protects the parathyroids and recurrent laryngeal nerves and the residual thyroid tissue can be ablated subsequently with radioactive iodine. Block dissection of lymphatic nodes is performed for clinically positive nodes only and not prophylactically.

FUNCTIONING GROUP

In regard to the group of functioning nodules, the policy adopted can be more flexible. Firstly, where the function of the nodule is shown to be equivalent to the rest of the gland, it is probable that the nodule is still dependent on the pituitary—thyroid axis via TSH, and may therefore be suppressible by the administration of thyroxine. If, on the other hand, there is already suppression of the rest of the gland and the nodule is hyperfunctioning or 'hot', then it is probable that, behaving autonomously in respect of thyroxine production, the nodule itself would not be suppressed by giving exogenous thyroxine.

A good indication of the suppressibility of a nodule may be gained from performing a suppression test and a suppression scan. For this purpose a tracer dose is given and the ^{131}I uptake is measured and a scintigram is performed. After the technique described by Werner and co-workers,[10] Greer,[11] thyroid is then administered in the form of 120 μg. of triiodothyronine daily for a period of 8 days. The uptake is then repeated. If the uptake has been suppressed by more than 50%, this indicates the expected result in a normal euthyroid subject and may also indicate suppressibility of the nodule, if taken in conjunction with the scintigram. The scan is also repeated after a period of attempted suppression with thyroxine or triiodothyronine. We have found the correlation between the suppression test and the suppression scan to be high. Thus, if a patient is euthyroid clinically and has a warm nodule with an uptake reading in the normal range and is suppressible by thyroxine, both as to uptake and on the scan, then this patient may be treated with thyroxine. Reports of success with this line of management are numerous in the literature,[12, 13] though a number of failures are also reported[4] and a critical assessment of this line of treatment is given by Badillo *et al.*[15] Our local experience has confirmed this in a number of cases which is, however, too small to be worth analyzing at this stage. We have observed, however, that the dosage required to achieve clinical shrinkage of the nodule may be as high as 0·8 mg. or more of thyroxine daily. This elevation of the dosage to the limits of tolerance, and the prospect of using the tablets permanently is found irksome by some patients who would prefer elective surgery.

If the nodule is hyperfunctioning or 'hot', the patient may or may not be toxic clinically.

(a) In the euthyroid group the patients may be observed over a period and thyroxine may be tried, but where the scan has shown evidence of autonomy and particularly where there has been failure of suppression on the 'Greer' test, there has not been response to ordinary doses of thyroid in our experience. Some of these patients become overtly toxic during the period of observation and they then fall into the next group.

(b) When *hyperthyroidism* is the presenting clinical sign and is confirmed by the usual tests, and a hyperfunctioning nodule is found on scintigram, then it is our usual practice to advise surgical removal of the nodule with a margin of 'normal' tissue—which usually implies subtotal lobectomy.

The histological appearances are demonstrated in Figs. 6 and 7 as seen in the hyperfunctioning nodule itself and in the adjacent suppressed tissue in such a case. The sections are taken from the gland of a patient who presented with a single nodule in the isthmus and clinical hyperthyroidism. The nodule was resected with a small margin of the adjacent normal gland. In Fig. 6 the hyperfunctioning tissue of the nodule can be seen with a high active type of epithelium lining small follicles with crenated colloid, while in the adjacent suppressed gland there is a flattened inactive epithelium and the follicles are distended with pooled colloid. The features of the hyperfunctioning area are confirmed in Fig. 7 under a higher magnification.

An alternate form of treatment with radioactive iodine is available, particularly when surgery has been decided against for some reason and provided that the patient does not fall into an age-group where this is contra-

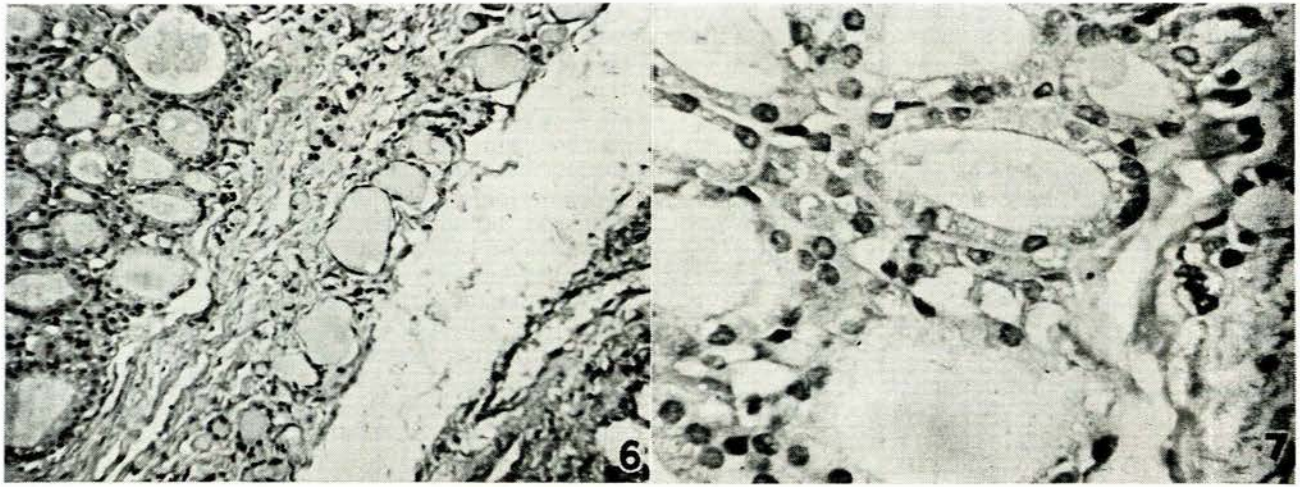


Fig. 6. The histological appearance of hyperfunctioning tissue lying adjacent to flattened inactive epithelium.
Fig. 7. The hyperfunctioning area under higher magnification.

indicated. There are many reports of successful ablation of hyperfunctioning nodules by this method, with subsequent recovery of function in the remainder of the gland.

The largest proportion of the hyperfunctioning nodules discovered at our clinic have been treated surgically. A small number have been given therapeutic doses of ^{131}I and good results have been obtained in these. A more careful assessment of the long-term outcome in relation to myxoedema and recurrence will have to be made before the relative merits of these forms of treatment can be evaluated in our own series.

SUMMARY

It is thought that where facilities are available, single thyroid nodules should be classified according to their capacity to take up radioactive iodine.

Surgical treatment is mandatory in the hypofunctioning group because of the high incidence of malignancy.

Patients with nodules that demonstrate function without inhibition of the rest of the gland may be treated with thyroid unless surgery is indicated by other symptoms.

The hyperfunctioning group do not respond to medication and apart from a small number treated with radioactive iodine, the majority are effectively treated by surgical removal.

Where no scintigram is available, surgical removal of all single nodules and a histological diagnosis is the safest policy.

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