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True Thyroid Adenoma

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SUMMARY

Clinical and isotopic characteristics of 138 patients with true thyroid adenoma are presented and analysed. Fifteen patients were hyperthyroid, 24 presented with borderline hyperthyroidism, and the remainder were euthyroid. Isotopically 20 adenoma were hyperfunctioning, 31 functioning, and 57 either hypo- or non-functioning. Isotopic status was not determined in the remaining 30.

Evidence is produced to show the value of a post-T_3 suppression, ^{131}I uptake in the evaluation of clinical status in borderline hyperthyroid patients with true thyroid adenoma. Approximately half such patients in this series were judged to be hyperthyroid in fact.

Females predominated over males in a ratio of 6:1. The age range was from 15 to 69, with a maximum incidence in the 35 to 65 age-groups. The percentage incidence by decades in active adenoma (hyperfunctioning and functioning) tended to lag behind that for inactive adenoma (hypo- and non-functioning) by about a decade, suggesting a tendency for inactive adenoma to become active with the passage of time.

The pathological nature of a consecutive series of 183 patients with single nodules is presented and analysed. An adenoma was found in 125, non-toxic nodular hyperplasia in 19. The nature was not determined in 32, leaving only seven due to other causes.

The pathological conditions found in a consecutive series of 438 patients with goitre are presented and analysed. Two hundred and thirty-five patients were suffering from hyperthyroidism or had an active adenoma; it is estimated that the incidence of hyperthyroid patients with adenoma was around 8 per cent of all hyperthyroid patients. One hundred and ninety-three patients presented with inactive adenoma or other non-toxic goitres. Adenoma accounted for 27 per cent.

The literature is reviewed and the clinical characteristics and problems of diagnosis and management of patients with true thyroid adenoma are discussed.

INTRODUCTION

The treatment of true thyroid adenoma is simpler and gives rise to less morbidity than that of nodular hyperplasia. The recognition of this condition is therefore

not a purely academic matter. Plummer writing in 1913 was apparently the first to recognize adenoma as a cause of hyperthyroidism distinct from toxic hyperplasia. A modern landmark was the paper by Cope, Rawson, and McArthur in 1947 who showed by autoradiographic studies in adenoma removed from patients treated by ^{131}I prior to enucleation that ^{131}I uptake was confined to the adenoma. Dobyns, Skanse, and Maloof (1949) first demonstrated the possibility of preoperative diagnosis by isotopic thyroid scanning.

The purpose of this paper is to report on the findings in a series of 138 patients with true thyroid adenoma and to review the literature.

MATERIALS AND METHODS

The adenoma were discovered among patients attending an Endocrine Clinic at this hospital. Most presented as single nodules but some were discovered when operating on patients with nodular hyperplasia. All but five were dealt with surgically and the diagnosis confirmed by macroscopic and microscopic findings; no thyroid lesion was accepted as an adenoma unless it presented a regular spherical or oval outline surrounded by a clearly defined capsule, and was clearly recognizable as distinct from the rest of the thyroid gland. Diagnosis in the other five rested upon good isotopic evidence; ^{131}I uptake was confined to the nodule and was not suppressed by pre-treatment with T_3; two were treated with ^{131}I and post-treatment studies in one showed some recovery of function in the remainder of the thyroid.

The special characteristics of thyroid adenoma were not appreciated until seven or eight years ago, and some of the earlier material had not been subjected to routine investigation. Latterly, however, all single nodules have been routinely subjected to ^{131}I uptake and scan; in nodules with active uptake the ^{131}I uptake and scan have been repeated following pre-treatment with T_3. The ^{131}I uptake and scan have again been studied subsequent to enucleation in all patients with nodules showing active uptake. PBI and T_3 resin uptake studies were carried out in a few patients with nodules showing active uptakes.

Two further studies were undertaken. The first was to determine the incidence of adenoma as the cause of a clinically single nodule. All single nodules have been indexed as such and the histological findings in a consecutive series of 183 such nodules have been determined. The second was to gain some idea of the incidence of adenoma in the goitre population as a whole. An index has been kept of all goitres seen with the exception of small goitres (an estimated 40 g or less) presenting at puberty, or reporting to their doctors with anxiety states at other ages and in whom the doctor had found such goitres and had required assurance of their lack of toxicity. The records of all such patients with indexed goitres seen in 1964 to 1968 have been studied. Flocculation tests have been carried out routinely in all patients with goitres. The diagnosis of auto-immune thyroiditis has been based mainly on the finding of a goitre combined with hypothyroidism or abnormally high flocculation findings; it has been confirmed in some instances by tests for thyroid antibodies and by biopsy. A few patients have been found accidentally at operation for believed non-toxic nodular hyperplasia.

DEFINITIONS

Various terms are used somewhat loosely in the literature, and it is necessary to define the meanings attached to them in this paper.

The distinction between nodule and adenoma would seem self evident; not all nodules, single or multiple, are adenomata, and adenomata are not always found as single nodules. The term nodule refers therefore to a clinical finding, that of adenoma to a pathological condition. Hyperthyroidism and euthyroidism refer to the clinical status of the patient. An important group of patients present with an equivocal clinical status; this is termed borderline hyperthyroidism.

TABLE 1. *Analysis of 138 patients with single and multiple adenoma, and whether these were in single or multiple nodular glands*

Number	Single nodule	Nodular goitre	Total
1	112	9	121
2	9	2	11
3+	5	1	6
Totals	126	12	138

A good classification for the isotopic activity of a nodule is that recently introduced by Meadows (1961 and 1962). He distinguishes hyperfunctioning, functioning, hypofunctioning, and non-functioning nodules. Hyperfunctioning nodules are those in which the production of iodothyronines is such as to have completely suppressed output by normal thyroid tissue shown on scanning. In functioning nodules output by the structure is high but normal thyroid tissue is still functioning in whole or in part. Output by the nodule is present but less than that from normal tissue in hypofunctioning structures. Non-functioning nodules are producing no iodothyronines. The first three groups are sometimes referred to as active, and the last as inactive.

Unfortunately we were unaware of the hypofunctioning group till late in our studies, and all such nodules were regarded as non-functioning. There can be little doubt therefore that our non-functioning group contains a proportion of hypofunctioning nodules. Furthermore, the term active in reference to our series covers hyperfunctioning and functioning nodules only, and the term inactive covers hypofunctioning and non-functioning structures.

FINDINGS

Mode of discovery. Most adenoma were discovered at operation on single nodules. A small proportion (about 1 in 10) were found at operation on diffuse or nodular thyroid hyperplasia. Details are shown in Table 1.

Multiple adenoma. The majority of adenoma were single, but a proportion (about 1 in 6) were multiple. Numbers exceeded two, however, in only 1:23 patients. Details are shown in Table 1.

Clinical status. The largest proportion of patients were euthyroid. Some were overtly toxic. The clinical status was equivocal in a significant proportion (about 1 in 6); this is an important group and must receive further study. Some were no doubt suffering from anxiety states but we believe that a proportion were indeed hyperthyroid.

TABLE 2. *Correlation between isotopic and clinical status of adenoma in 138 patients*

	Eu	? Hyper	Hyper	Total
Hyper-functioning	1	7	12	20
Functioning	20	10	1	31
Non-functioning	51	5	1*	57
Undetermined	27	2	1	30
Totals	99	24	15	138

* A non-functioning nodule in toxic hyperplasia.

Correlation of clinical and isotopic status. Table 2 shows the correlation between the clinical and isotopic status in patients in whom both features are known. It is clear that overt hyperthyroidism was mostly associated with hyperfunctioning adenoma, while non-functioning adenoma were mostly associated with euthyroidism. What is of special interest is the relation of equivocal clinical status to isotopic activity; only one out of 11 patients with non-functioning nodules were suspected of hyperthyroidism, the proportion rising to one in three of patients with hyperfunctioning or functioning nodules. This raises the suspicion that some of the latter group were indeed hyperthyroid, and further study tended to bear this out.

Twenty-four-hour ^{131}I *uptake and results of suppression tests.* The 24-hour ^{131}I uptakes for euthyroid, equivocally and frankly hyperthyroid patients with hyperfunctioning and functioning adenomata are contrasted with the findings for euthyroid controls and patients with toxic hyperplasia in Fig. 1. It will be noted that most of the adenoma patients with euthyroid and equivocal status and a significant number of those with overt hyperthyroidism have ^{131}I uptakes which fall into the range for euthyroid controls. A different picture however emerges when the results of suppression tests are studied (Fig. 2). It should be noted that zero suppression is at the top of the ordinate scale and 100 per cent at the bottom; this is an attempt to give a visual demonstration of the degree of suppression. All the hyperthyroid patients, more than half of those with equivocal status, and even one euthyroid patient, now fall into the hyperthyroid range. It is concluded that many patients with hyperfunctioning and functioning adenoma had actual or borderline hyperthyroidism, and in particular that *approximately half the patients with such adenoma and of equivocal clinical status were in fact hyperthyroid.*

PBI and T_3 *resin uptake findings.* In overtly hyperthyroid patients two PBI assays were in the normal and two in the hyperthyroid range; two T_3 resin uptake assays were in the hyperthyroid range. In the equivocal and euthyroid groups with active adenoma seven PBI assays and seven T_3 resin uptake findings were within the normal ranges.

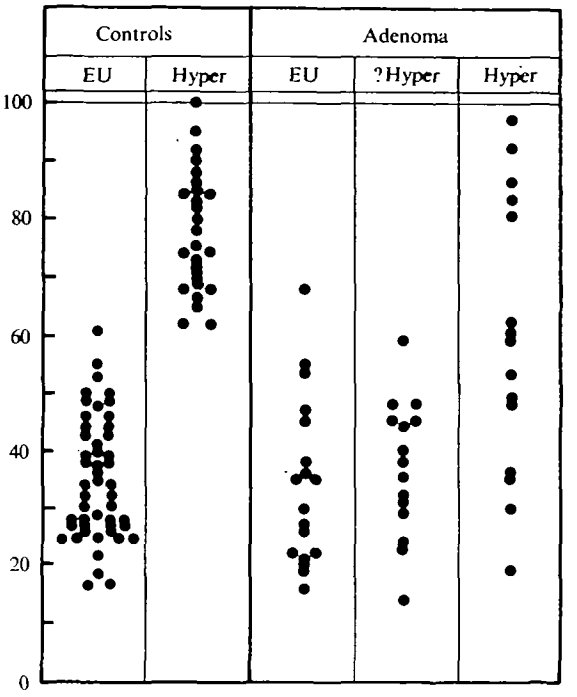

FIG. 1. Per cent 24-h ^{131}I neck uptake for euthyroid control patients, patients with hyperthyroidism due to generalized hyperplasia, and euthyroid, borderline hyperthyroid and hyperthyroid patients with adenoma.

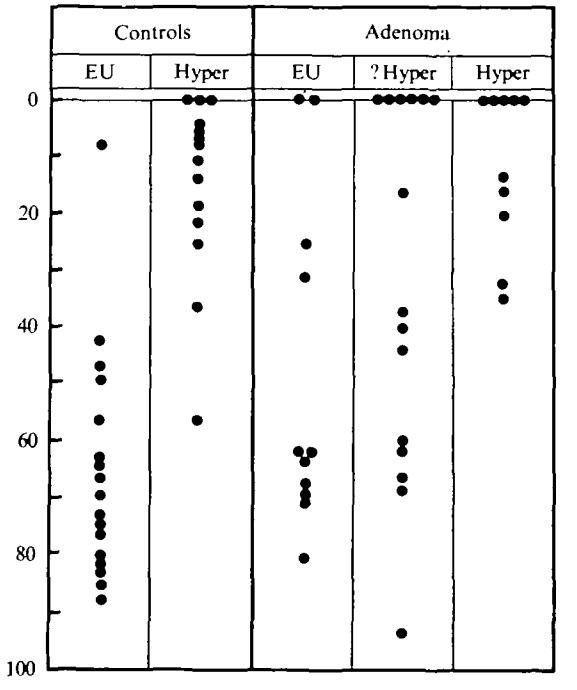

FIG. 2. Per cent 24-h ^{131}I neck uptake suppression following T_3 in euthyroid control patients, patients with hyperthyroidism due to generalized hyperplasia, and euthyroid, borderline hyperthyroid, and hyperthyroid patients with adenoma.

Sex incidence. The sex incidence for both active and inactive adenoma are shown in Table 3. Females outnumber males by about 6 to 1, and there is no obvious distinction in this respect between active and inactive forms.

TABLE 3. *Sex incidence*

	Males	Females
Active	7	45
Inactive	8	50
Undetermined	4	24
Total	19	119

Age incidence. The age incidence of active and inactive adenoma were studied separately for men and women; no obvious differences in pattern were noted. The figures for both men and women have therefore been put together and the percentage incidence by decades from 5 to 75 for active and inactive adenoma are shown in Fig. 3. It would appear that active adenoma tend to appear some 10 years later than inactive adenoma, raising the possibility that a proportion of inactive adenoma will eventually become active.

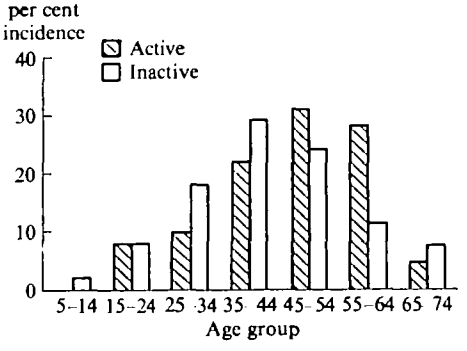

FIG. 3. Percentage age incidence of patients with active and inactive adenoma.

Pathological nature of single nodules. Not all single nodules are adenomatous in nature. Table 4 shows the findings in a consecutive series of 183 single nodules. Much the largest group consisted of true adenoma—125. The next commonest was adenomatous hyperplasia. The frank encapsulation of the two cysts, and the widely varying degree of cystic change found in undoubted adenoma suggests that these cysts commonly represent the final stage of degeneration in adenoma. Only two patients in this series were suffering from carcinoma. The cause was undetermined in 32 patients.

The isotopic activity was known in 122 of these 183 patients, and it was possible to correlate isotopic activity with the histological findings in 108. The results are shown in Table 5 and present no surprises.

TABLE 4. *Pathological nature of 183 patients with single thyroid nodules*

Nature	Number
Adenoma	125
Adenomatous hyperplasia	19
Carcinoma	2
Auto-immune thyroiditis	2
Cysts of undetermined origin	2
Tuberculosis of cervical gland	1
Undetermined	32

TABLE 5. *Pathological nature of single nodules in those patients where the isotopic activity was known*

Nature	Active	Inactive
Adenoma	45	49
Adenomatous hyperplasia	7	7
Carcinoma	..	2
Auto-immune thyroiditis	..	2
Cysts of undetermined origin	..	2
Tuberculosis of cervical glands	..	1
Undetermined	7	7

TABLE 6. *Analysis of 438 consecutive patients with goitre*

Hyperplasia		298
Adenoma		97
Activity determined	91	
Activity not determined	6	
Possible adenoma		14
Other goitres		29

TABLE 7. *Analysis of patients with non-toxic goitres including inactive adenoma*

Non-toxic hyperplasia	101
Inactive adenoma	53
Auto-immune thyroiditis	19
Carcinoma	6
Cysts	4

Incidence of adenoma in the total goitre population. A consecutive series of 438 patients with goitre observed between 1964 and 1968 have been analysed. The over-all picture is shown in Table 6. Patients with non-toxic hyperplasia, inactive adenoma, and other non-toxic disorders are analysed in Table 7, and patients

with toxic hyperplasia and active adenoma in Table 8. The high proportion of patients with inactive adenoma in the non-toxic group (between 1 in 3 and 1 in 4) is interesting and perhaps a little surprising. Of particular concern is the incidence of hyperthyroidism due to adenoma. If those with overt hyperthyroidism are

TABLE 8. *Analysis of patients with toxic hyperplasia or active adenoma*

Toxic hyperplasia		197
Active adenoma		
Euthyroid	12	
? Hyperthyroid	16	
Hyperthyroid	10	
Total adenoma		38

considered the incidence is about 1 in 20. However, it was concluded in the section above on the results of 24-hour ^{131}I uptake and suppression tests, that approximately half the patients with equivocal clinical status are in fact suffering from hyperthyroidism. *If such a calculation is applied to the figures in Table 8 the incidence of hyperthyroidism due to thyroid adenoma rises to around* 1 in 12. It is obviously worth while therefore keeping a look out for such cases.

^{131}I *therapy*. Two patients only were treated with ^{131}I. Both became euthyroid after 25 and 35 mCi respectively.

DISCUSSION

A number of papers reporting on series of adenoma patients have now appeared and important features associated with thyroid adenoma are becoming clearly defined. The papers vary in value with the criteria used for making the diagnosis of adenoma. The most valuable are those in which the diagnosis is firmly based on pathological findings after removal of the adenoma (Alivisatos, Georgiadou, and Giannatos, 1965; Cope, Rawson, and McArthur, 1947; DeCourt, Savoie, de Gennes, and Jungers, 1962; Demeester-Mirkine and Ermans, 1967; Dobyns and Lennon, 1948; Garnier, Reynier, Savoie, Calmettes, Meillère, and Cordier, 1964; Greene, 1957; Lobo, Rosenthal, and Fridman, 1965; Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Meadows, 1961, 1962; Molnar, Wilber, Lee, Woolner, and Keating, 1965; Savoie, 1961; Vague, Simonin, Miller, and Alland, 1965). Slightly less valuable are those in which the diagnosis is based on the demonstration that the nodules are autonomous, that uptake of radioactive iodine by the nodules cannot be suppressed by T_3, and sometimes by the return of uptake in normal tissue following successful therapy (Sheline and McCormack, 1960; Silverstein, Burke, and Cogan, 1967; Skillern, McCullagh, and Clamen, 1962).

Diagnosis. It is generally believed that only nodules due to adenoma (or active carcinoma) are autonomous and that uptake in nodules due to other causes can be suppressed; this is probably correct but more evidence in the latter type of nodule would be helpful. It should be possible therefore to establish the diagnosis

of active adenoma (or carcinoma) in all instances by performance of thyroid scans with ^{131}I before and after the use of T_3, and indeed uptake in the nodule is not abolished in hyperfunctioning and functioning adenoma. The initial scan can be unhelpful in distinguishing between hypofunctioning and functioning nodules since the limited uptake in hypofunctioning adenoma is mimicked by that in normal tissue surrounding non-functioning forms. The suppression test technique should help in this situation, but the authors know of no instance in which this has been used. The adenomatous nature of a non-functioning nodule cannot of course be decided on the results of scanning since autonomy cannot be demonstrated.

The diagnosis of hyperthyroidism in adenoma presents difficulties. All authors agree that the degree of hyperthyroidism found with adenomata is, generally speaking, distinctly less than that in diffuse hyperplasic goitres. We found that the hyperthyroidism in a significant proportion (around one sixth) of our patients with hyperthyroidism due to adenoma was clinically borderline in character, and this has been noted by others (DeCourt, Savoie, de Gennes, and Jungers, 1962; Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Savoie, 1961; Sheline and McCormack, 1960; Vague, Simonin, Miller, and Alland, 1965). Moreover, tests of thyroid function may be normal even in patients with clinically overt hyperthyroidism (DeCourt, Savoie, de Gennes, and Jungers, 1962; Fellinger, Höfer, Egert, and Vetter, 1961; Molnar, Childs, and Woolner, 1958; Skillern, McCullagh, and Clamen, 1962; Vague, Simonin, Miller, and Alland, 1965). The neck uptake of radioactive iodine and the PBI are particularly likely to be within normal limits (DeCourt, Savoie, de Gennes, and Jungers, 1962; Fellinger, Höfer, Egert, and Vetter, 1961; Molnar, Childs, and Woolner, 1958; Skillern, McCullagh, and Clamen, 1962; Vague, Simonin, Miller, and Alland, 1965). The 48-hour PBI 131, on the other hand, is a more reliable guide (Alivisatos, Georgiadou, and Giannatos, 1965; Demeester-Mirkine and Ermans, 1967; Fellinger, Höfer, Egert, and Vetter, 1961; Malamos, Koutras, Fringeli, and Tassopoulos, 1969). The explanation of these findings is obscure. An abnormality in the size of the thyroid pool has been suggested (Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Vague, Simonin, Miller, and Alland, 1965) but it is difficult to see how such an explanation would fit the facts. A more consistent hypothesis is that the T_3/T_4 production ratio is higher with adenoma than in normal subjects (McConnon, Row, and Volpé, 1970). The T_3 suppression of neck uptake of radioactive iodine appears to us a much more reliable guide and this has been the experience of others (Demeester-Mirkine and Ermans, 1967; Molnar, Childs, and Woolner, 1958). It is invariably impaired in hyperfunctioning adenoma, but may be within the normal range in functioning adenoma, as might be expected since much of the iodothyronine production may be coming from normal tissue in the latter group. Nevertheless, it should be noted that patients with hyperfunctioning adenoma may be euthyroid (DeCourt, Savoie, de Gennes, and Jungers, 1962; Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Molnar, Wilber, Lee, Woolner, and Keating, 1965; Savoie, 1961; Sheline and McCormack, 1960; Vague, Simonin, Miller, and Alland, 1965), and our evidence suggests that some patients with functioning adenoma may evidence borderline hyperthyroidism.

Significance of activity. Non-functioning adenoma are regarded as 'inactive'. Field, Yamashita, DeRubertis, and Dekker (1970), however, found that the activity of six enzyme systems in non-functioning adenoma were at or even above normal limits. The 'inactivity' appears therefore to be confined to iodine-processing mechanisms.

Incidence of single and multiple adenoma and association with other conditions. Adenoma are normally single but may be multiple (Alivasatos, Georgiadou, and Giannatos, 1965; Cope, Rawson, and McArthur, 1947; DeCourt, Savoie, de Gennes, and Jungers, 1962; Dobyns and Lennon, 1948; Garnier, Reynier, Savoie, Calmettes, Meillère, and Cordier, 1964; Lobo, Rosenthal, and Fridman, 1965; Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Savoie, 1961). The incidence of multiple adenomata has ranged in the various reported series from 8 per cent (Garnier, Reynier, Savoie, Calmettes, Meillère, and Cordier, 1964) to 25 per cent (Lobo, Rosenthal, and Fridman, 1965). Adenomata usually present as isolated nodules but may be found in association with other conditions such as nodular hyperplasia.

Age and sex incidence. Adenoma occurs at all ages, the reported age range being from 15 to 69 with the maximum incidence in the 30 to 60 age-group (DeCourt, Savoie, de Gennes, and Jungers, 1962; Garnier, Reynier, Savoie, Calmettes, Meillère, and Cordier, 1964; Lobo, Rosenthal, and Fridman, 1965; Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Savoie, 1961; Vague, Simonin, Miller, and Alland, 1965). Thyroid nodules may antedate the appearance of hyperthyroidism by many years, figures of up to 30 being recorded (DeCourt, Savoie, de Gennes, and Jungers, 1962; Fellinger, Höfer, Egert, and Vetter, 1961; Lobo, Rosenthal, and Fridman, 1965; Molnar, Wilber, Lee, Woolner, and Keating, 1965; Vague, Simonin, Miller, and Alland, 1965). This has led to the suggestion that inactive or at least sub-clinically active adenoma may evolve into adenoma with overt hyperthyroidism. Our data for the percentage incidence of active and inactive adenoma are consistent with this hypothesis, and this transformation has in fact been observed (Lobo, Rosenthal, and Fridman, 1965; Vague, Simonin, Miller, and Alland, 1965). On the other hand, the frequency with which degenerative processes are observed in thyroid adenoma suggest that active adenoma could become generally less active as the years go by, and this transformation has also been observed (Silverstein, Burke, and Cogan, 1967).

Females greatly predominate over males, and outnumbered males by 6:1 in our series. Ratios of from 4 to 20:1 have been recorded in the literature (DeCourt, Savoie, de Gennes, and Jungers, 1962; Garnier, Reynier, Savoie, Calmettes, Meillère, and Cordier, 1964; Lobo, Rosenthal, and Fridman, 1965; Malamos, Koutras, Fringeli, and Tassopoulos, 1969; Savoie, 1961; Vague, Simonin, Miller, and Alland, 1965).

Pathological nature of single nodules. The nature of the single nodule is an important clinical problem. Though adenoma are commonly single, it by no means follows that all single nodules are adenoma. Single nodules due to nodular hyperplasia, auto-immune thyroiditis, carcinoma, cysts, and other less-common abnormalities have been noted in this and other series (Greene, 1957; Meadows,

1961, 1962). Cysts and carcinoma are usually isotopically inactive, but single nodules due to nodular hyperplasia or auto-immune thyroiditis may be active or inactive.

Incidence of carcinoma in single nodules. The possibility of a single nodule being carcinomatous is a matter of particular concern to clinicians. Many papers have been written on the subject (Attie, 1960; Beahrs, Pemberton, and Black, 1951; DeCourt, Savoie, de Gennes, and Jungers, 1962; Dische, 1964; Grant, Canter, and Lenhardt, 1963; Greene, 1957; Groesbeck, 1959; Johnson and Beierwaltes, 1955; Kendall and Condon, 1969; Lahey and Hare, 1951; Majarakis, Slaughter, and Cole, 1953; Meadows, 1961, 1962; Perlmutter and Slater, 1956) and there is substantial agreement on the findings. Hyperfunctioning nodules are rarely carcinomatous, recorded incidences being usually below 1 per cent. However, they are not unknown and cases with overt hyperthyroidism even have been recorded (Beahrs, Pemberton, and Black, 1951; Becker, Economou, and Schwartz, 1963; Dische, 1964; Lahey and Hare, 1951; Majarakis, Slaughter, and Cole, 1953; Meadows, 1962; Molnar, Wilber, Lee, Woolner, and Keating, 1965; Seidlin, Marinelli, and Oshry, 1946). The incidence of carcinoma in functioning nodules is low but significant, in the order of 5 per cent. The incidence in inactive nodules is, however, much higher, figures given ranging from 15 to 30 per cent. The number of papers in which a distinction is clearly made between hypo- and non-functioning nodules is limited (Grant, Canter, and Lenhardt, 1963; Meadows, 1961, 1962), but it appears that the incidence of carcinoma in the former may be little higher than that for functioning nodules—in the order of 7 to 8 per cent. Meadows (1962) who made such a distinction then found an even higher incidence of carcinoma in non-functioning nodules, namely 55 per cent.

Incidence of adenoma as a cause of hyperthyroidism. The incidence of adenoma as a cause of hyperthyroidism is of some interest. It is generally considered distinctly low, but there are indications that this is not entirely correct. Reference to Table 8 shows that the incidence of overt hyperthyroidism in a consecutive unselected series of hyperthyroidism was 4·3 per cent. Roualle (1948–9), Vague, Simonin, Miller, and Alland (1965), and Malamos, Koutras, Fringeli, and Tassopoulos (1969) report figures in the order of 4, 13, and 6 per cent respectively. However, there was a significant group of patients with borderline hyperthyroidism in our series of adenoma subjects; comparison of ^{131}I neck uptakes before and after T_3 showed that suppression was in the hyperthyroid range in approximately half (Fig. 2). If half the patients with borderline hyperthyroidism in the consecutive unselected series of hyperthyroid patients (Table 8) are regarded as hyperthyroid, the incidence of hyperthyroidism due to adenoma rises to 7·7 per cent. Vague, Simonin, Miller, and Alland (1965) and Malamos, Koutras, Fringeli, and Tassopoulos (1969) also noted the existence of borderline patients. It is possible therefore that the true incidence of hyperthyroidism due to adenoma lies between 5 and 10 per cent. The matter is not entirely academic since the morbidity from simple enucleation or ^{131}I therapy of an adenoma is less than that from partial thyroidectomy or ^{131}I therapy for hyperthyroidism due to generalized hyperplasia.

Incidence of inactive adenoma. The incidence of single inactive adenoma in our consecutive series of euthyroid patients with goitre was surprisingly high—in the order of 35 per cent (Table 7). A somewhat similar figure can, however, be deduced from the figures for single nodules in a similar series reported by Perlmutter and Slater (1956).

Treatment. The therapeutic problem is largely that of the action to be taken on finding a solitary nodule in the thyroid. Isotopic studies are helpful and patients can be divided into those with active and unsuppressible nodules (adenoma or carcinoma), those with active but suppressible nodules, and those with non-functioning nodules.

A choice of therapy is available for those with active non-suppressible nodules. Enucleation is minimally traumatic and permits histological examination of the nodule. DeCourt, Savoie, de Gennes, and Jungers (1962) claim that preparation of the patient with anti-thyroid drugs is unnecessary since they have never seen crisis following operation for adenoma. The authors have however seen one such case, and in any case consider that restoration to a euthyroid state in overtly hyperthyroid patients prior to operation desirable. They use anti-thyroid drugs in frankly hyperthyroid subjects, and iodine in mildly affected or borderline patients. ^{131}I is taken up selectively by hyperfunctioning adenoma; hypothyroidism is not a danger since normal thyroid tissue is undamaged and recovers function following destruction of the adenoma. ^{131}I therapy can also be given to other active adenoma provided the patient is pre-treated with T_3 to suppress ^{131}I uptake by normal thyroid tissue. Rather higher doses seem to be needed than for toxic hyperplasia—in the order of 20 to 40 mCi (Becker, Economou, and Schwartz, 1963; Demeester-Mirkine and Ermans, 1967; Greene, 1957; Groesbeck, 1959) though several authors have managed with less (Molnar, Wilber, Lee, Woolner, and Keating, 1965; Roualle, 1948–9; Skillern, McCullagh, and Clamen, 1962). The adenoma usually shrinks considerably with such treatment but by no means always disappears (Demeester-Mirkine and Ermans, 1967; Molnar, Wilber, Lee, Woolner, and Keating, 1965; Roualle, 1948–9).

The high incidence of carcinoma in non-functioning nodules clearly calls for surgery. Active but suppressible nodules may be dealt with surgically or by suppression with T_4 in an attempt to promote regression depending upon the merits of each case. The authors believe that non-suppressible functioning and hypofunctioning nodules should be dealt with surgically. Hyperthyroidism may evolve in untreated euthyroid patients. The incidence of carcinoma though low is not negligible. Nodules treated with ^{131}I may become non-functioning and it is conceivable that this may render them liable to malignant change. Surgery or ^{131}I therapy are both legitimate for hyperfunctioning nodules. The danger of such nodules being carcinomatous is negligible, and of their being rendered non-functioning and potentially malignant is hypothetical. The authors in fact prefer enucleation, reserving ^{131}I therapy for elderly or poor risk cases. If ^{131}I therapy is chosen prolonged morbidity from persisting hyperthyroidism should be avoided by giving high doses—in the order of 30 to 40 mCi.

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