Pituitary, adrenal and thyroid incidentalomas

H E Turner, N R Moore, J V Byrne and J A H Wass

Departments of Endocrinology and Radiology, Radcliffe Infirmary and University of Oxford, Woodstock Road, Oxford OX2 6HE UK

Introduction

The use of increasingly sophisticated imaging techniques has produced a new clinical problem; namely the evaluation and management of the serendipitously discovered mass - 'incidentaloma'. In the last 50 years of endocrinology, these lesions have been described mainly in the adrenal and pituitary glands by pathologists on the basis of autopsy studies of patients assumed to have been asymptomatic. The current challenge is the investigation of these lesions, which are now more frequently detected during life, to allow not only the correct identification and investigation of those with a hypersecretory syndrome, whether it be clinically apparent or subclinical, but also the correct identification of those masses which are malignant and which may therefore produce significant problems in the future. As more experience is gained on the natural history of the true incidentaloma, appropriate follow-up and treatment can be instigated as necessary. The rationale of investigations therefore should be to evaluate most accurately and cost-effectively which patients do not have an incidentaloma, but a lesion that requires further active treatment.

Terminology may be confusing, as 'incidentaloma' and 'incidentally discovered', and 'subclinical' have been used, often interchangeably in this context. While a pituitary macroadenoma or adrenal carcinoma may be incidentally discovered, we believe that they should not be described as incidentalomas. This term should be reserved for those lesions which are incidentally discovered, that have no associated hormonal hyper- or hyposecretion, and that have a benign natural history. The incidental radiological discovery of a mass may be one of clinical relevance in a patient for example subsequently found to be hyperprolactinaemic, although hitherto asymptomatic - perhaps a better term for these lesions is 'subclinical' to differentiate them from the true incidentaloma.

Pituitary

Epidemiology

The vast majority of pituitary incidentalomas are microadenomas (<1 cm in diameter). Their reported prevalence depends on the method of detection - whether it is based on an autopsy series of patients assumed to be asymptomatic, or on a series of patients undergoing imaging of the head.

Autopsy studies

In 1936, Costello published the results of an examination of 100 pituitary glands at post-mortem, in which small adenomas were found in 22.5% of cases using sections of up to 1.5 mm in size (Costello 1936). Costello called these tumours 'subclinical adenomas' and found them to be equally distributed between the sexes. They become more common with increasing age (Parent et al. 1981). Other autopsy studies have shown that between 1.5 and 26.7% of pituitaries examined in subjects not suspected of having pituitary disease harbour adenomas (Molitch & Russell 1990). The reason for this wide variation in frequency may partly be due to different slice thickness used to examine the pituitary. The majority of studies suggest a frequency of between 10 and 20%. A recent study of 1000 pituitary glands using the same section thickness as Costello found incidental lesions in 178 (18%) glands, and in one-third these were >2 mm in diameter (Teramoto et al. 1994). The lower prevalence of incidental findings in this study compared with the Costello data may in part be due to classification of areas of hyperplasia as adenomas in the original paper. An analysis of 12 autopsy studies reported that there were only three incidental macroadenomas detected (all <15 mm), out of a total of 9737 pituitaries examined (Molitch & Russell 1990). Interestingly two of these larger tumours were found in the series of patients aged over 80 at post-mortem (Kovacs et al. 1980). This series showed a frequency of pituitary adenomas of 13%, and 9 out of the 17 adenomas examined (53%) immunostained for prolactin (PRL).

Therefore, pituitary microadenomas are a common finding at autopsy, and appear to become commoner with increasing age. Incidental macroadenomas are in contrast uncommon, and also appear to be commoner in older age-groups.
Imaging studies

The detection of incidental pituitary lesions on imaging depends on the technique, use of contrast agents, and the slice thickness used. The true prevalence of asymptomatic adenomas is probably higher than detected in many imaging studies, because of the limited sensitivity of magnetic resonance imaging (MRI) for small tumours, and this may explain why the reported prevalence is higher in an autopsy population. This is illustrated by a recent autopsy study of 1000 pituitary glands, where 178 (18%) glands harboured incidental tumours, but only 61 (6%) were >2 mm in size and thus likely to be visible on computed tomography (CT) or MRI (Teramoto et al. 1994). MRI with gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) administration demonstrated asymptomatic pituitary adenomas in 10% of normal volunteers aged 18-60 years (Hall et al. 1994). A study using CT scans with contrast enhancement identified probable adenomas in 12/107 (11.2%) normal women (Wolpert et al. 1984). Chong et al. (1994) found focal pituitary hypointensities in 40% of healthy volunteers on T1-weighted spin echo MRI, but found that in the majority they could be differentiated from pituitary microadenomas by their smaller size and less marked degree of signal difference relative to the pituitary gland.

Incidental pituitary macroadenomas have occasionally been reported, where a tumour >1 cm in diameter has been detected when imaging for non-endocrine indications, for example a head injury or seizures (Chacko & Chandy 1992). However, these are not true incidentalomas, as illustrated by a series of five cases, where three patients had hypopituitarism and four of the patients underwent surgery (Chacko & Chandy 1992). Reincke et al. (1990) report 18 patients with ‘incidentalomas’ of the pituitary. Four patients in this series required neurosurgery - two because of visual field defects, one because of displacement of the chiasm by the tumour, and one who had biochemical evidence of acromegaly. Three of the cases not requiring neurosurgery - two because of visual field defects, one because of displacement of the chiasm by the tumour, and one who had biochemical evidence of acromegaly. Three of the cases not requiring neurosurgery were luteinising hormone/follicle-stimulating hormone deficient. It is therefore incorrect in our view to describe all these tumours as true incidentalomas. Four of the truly asymptomatic patients had mesoadenomas (tumour diameter 11-20 mm) and showed no increase in tumour size during follow-up. All the patients with microadenomas that had been detected incidentally on imaging for reasons such as vertigo, concussion and syncope, were asymptomatic with normal pituitary function, and no visual field abnormalities.

Thus after detailed endocrine and visual examination, macroadenomas, even if they present serendipitously, have usually produced significant effects, mesoadenomas may do so and microadenomas have rarely done so.

Pathology

Positive immunostaining for PRL was shown in 34/81 adenomas (42%) in an analysis of pituitary adenomas detected at autopsy (Molitch & Russell 1990). McComb et al. (1983) compared the pattern of immunostaining of the tumours found at autopsy with those removed surgically, and showed that there was a marked difference (Table 1). The majority in the subclinical autopsy series were negative (54%) or PRL staining (42%) whereas only 25% of the surgical series were null cell adenomas and 29% PRL staining. There was a higher number of growth hormone (GH) positive, adrenocorticotrophin (ACTH) and mixed GH/PRL staining adenomas in the surgical series (McComb et al. 1983). This difference is obviously in part due to the fact that prolactinomas often do not require surgery, and also because the secretory tumours are likely to present with clinical effects during life.

It is not uncommon for multiple adenomas to be detected in the pituitaries found to harbour incidentalomas - 3/42 subjects in one study (Parent et al. 1981), 2/20 in another (Kovacs et al. 1980) and 7/100 subjects in another (McComb et al. 1983). The significance of this is unclear, but the tumours do not necessarily have the same immunostaining characteristics.

Natural history

Follow-up data of incidentally detected microadenomas show that they very rarely show significant enlargement, whereas larger incidentalomas are more likely to enlarge (Table 2). The data from Reincke et al. (1990) show that

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Table 1 Pattern of immunostaining of pituitary tumours found at autopsy and removed surgically.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Negative</th>
<th>PRL positive</th>
<th>GH positive</th>
<th>ACTH positive</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy</td>
<td>42% (34/81)</td>
<td></td>
<td></td>
<td></td>
<td>Molitch &amp; Russell (1990)</td>
</tr>
<tr>
<td>Autopsy</td>
<td>41% (7/17)</td>
<td>55% (9/17)</td>
<td>1 GH and PRL</td>
<td>0</td>
<td>Kovacs et al. (1980)</td>
</tr>
<tr>
<td>Autopsy</td>
<td>50% (54/107)</td>
<td>42% (45/107)</td>
<td></td>
<td></td>
<td>McComb et al. (1983)</td>
</tr>
<tr>
<td>Surgical</td>
<td>25.1% (152/606)</td>
<td>29% (176/606)</td>
<td>16.2% (98/606)</td>
<td>8.4% (51/606)</td>
<td>McComb et al. (1983)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PRL and GH 9.2% (56)</td>
<td>Silent 8% (36)</td>
<td></td>
</tr>
</tbody>
</table>
during a mean follow-up of 30 months (range 12-96), only one of seven patients with incidentally detected microadenomas showed tumour enlargement from 5 to 9 mm (Reincke et al. 1990) (Table 2). One of the four patients with a larger (11-20 mm in diameter) incidentaloma, with normal visual fields, showed tumour enlargement from 14 to 20 mm during mean follow-up of 26 months (range 17-48). Neither of these patients required any intervention. Thirty-one patients with incidentally discovered pituitary masses (15 microadenomas and 16 larger ones of 11-20 mm diameter), with no significant endocrinopathy or reduction in visual fields, were followed up for a mean of 6.4 years (range 3-11 years). Only 1/16 patients with macroadenomas developed tumour enlargement (15 mm increasing to 20 mm) which required surgery because of visual field change; 4 others showed enlargement in the diameter of the tumour by 1-2 mm (Donovan & Corenblum 1995). One patient with a macroadenoma of diameter 17 mm developed apoplexy while heparinised for a coronary angiogram. Of the 15 patients with incidentally detected microadenomas, only one tumour enlarged and only by 1 mm (from 4 to 5 mm) during a 5 year follow-up.

More data are required to confirm the natural history of these tumours, but, from these small studies, it is likely that microincidentalomas follow a benign course and there are no data to suggest that these will lead to any form of endocrinopathy. On the other hand incidentally detected macroadenomas may enlarge in size and require surgery - and therefore the term incidentaloma should only be used for those tumours over 10 mm in diameter that remain intra-sellar, often referred to as mesoadenomas.

There are data showing that hyperprolactinaemia will be self-limiting in up to one-third of women affected and that pregnancy may be one feature that will trigger a return to normal function (Jeffcoate et al. 1996). It would be useful to know more about the natural history of pituitary microincidentalomas, particularly whether there is a significant rate of spontaneous resolution, as the autopsy studies show that at least one-third of these tumours are prolactinomas.

**Differential diagnosis**

It is clearly important that the incidentally detected pituitary lesion is evaluated appropriately and differential diagnoses considered such as cranio-pharyngioma, metastasis or an inflammatory process (Soule & Jacobs 1996).

**Features**

By definition, a patient with a true incidentaloma should be asymptomatic. Headache is a symptom for which MRI/CT scanning is performed and incidental pituitary adenomas are sometimes detected in these patients. Does this mean that these patients are symptomatic of the tumour? Unless the adenoma is large and causing visual symptoms, headache is not a usual feature of these tumours as an isolated finding and is therefore not attributable to pituitary microadenomas (Reincke et al. 1990).

In the series of incidentalomas detected using MRI in normal volunteers, there was no evidence of endocrinopathy in any of the patients with adenomas (Hall et al. 1994). The difference in prevalence of null cell adenomas and prolactinomas when incidentalomas are compared with clinical series is likely to be due to the relatively early detection of adenomas secreting GH or ACTH due to the associated clinical syndromes. Clearly, tumours leading to acromegaly or Cushing’s syndrome, even if detected incidentally, cannot be defined as incidentalomas.

It is possible that an incidentaloma may masquerade as the cause of a patient’s disease. At our institution we have seen two patients in the last year with pituitary

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**Table 2 Follow-up data for incidentally detected pituitary adenomas.**

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>Reference</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Number which enlarged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microadenoma (&lt;11 mm)</td>
<td>Reincke et al. (1990)</td>
<td>7</td>
<td>30 months (12-96)</td>
<td>1 (5 → 9 mm)</td>
</tr>
<tr>
<td>Microadenoma (&lt;11 mm)</td>
<td>Donovan &amp; Corenblum (1995)</td>
<td>15</td>
<td>6.4 years (3-11)</td>
<td>1 (4 → 5 mm)</td>
</tr>
<tr>
<td>Macroadenoma (11-20 mm)</td>
<td>Reincke et al. (1990)</td>
<td>4</td>
<td>26 months (17-48)</td>
<td>1 (14 → 20 mm)</td>
</tr>
<tr>
<td>Macroadenoma (11-20 mm)</td>
<td>Donovan &amp; Corenblum (1995)</td>
<td>16</td>
<td>6.4 years (3-11)</td>
<td>5 (by 1-5 mm)</td>
</tr>
</tbody>
</table>
microadenomas initially thought to be the cause of their Cushing’s syndrome, who actually turned out to have ectopic and adrenal origins of their disease (Fig. 1).

Investigation
Investigation must be directed towards determining whether the pituitary lesion is functioning and producing hormone, and secondly whether there is any evidence of hyposecretion of hormones from the remainder of the pituitary gland. Hypopituitarism is very unusual with microadenomas. However, microadenomas may secrete PRL, GH, ACTH or thyroid-stimulating hormone (TSH), and be associated with a typical clinical syndrome. These conditions therefore need screening and treating appropriately with medication or surgery. The most cost-effective means of investigation for hormonal hypersecretion have been advocated to include two or three PRL measurements for prolactinoma (Molitch 1995); insulin-like growth factor-I may act as a screen for acromegaly, although if the diagnosis is suspected a formal oral glucose tolerance test should be performed; 24 h urinary free cortisol and overnight dexamethasone suppression testing are useful screening tests for the diagnosis of Cushing’s disease; and an unsuppressed TSH in the presence of elevated free thyroid hormone levels is the marker of the rare TSH secreting tumour. Others suggest that although some form of biochemical screening for acromegaly and Cushing’s disease is usually performed in these cases, this approach may be over cautious (Soule & Jacobs 1996). In the series reported by Donovan & Corenblum (1995), the patient evaluation included a clinical assessment and serum PRL, but no formal biochemical assessment for acromegaly or Cushing’s syndrome. No syndromes of hormone excess developed during a mean follow-up of 6.4 years. Similar conclusions were reached in a recent cost-effectiveness analysis where four different management strategies were compared for a patient with an incidentally detected asymptomatic pituitary adenoma (King et al. 1997). Most endocrinologists, in view of the limited long-term data in this condition, will consider excluding all hypersecreting syndromes, and we subscribe to this view.

Patients with incidentally detected macroadenomas need to be investigated in the same way; both for hormonal hypersecretion, when definitive treatment is indicated anyway, and also for hypopituitarism, which is uncommon with these larger tumours. Visual field assessment should be carefully performed as these will need to be monitored as the tumour has already demonstrated its capability to grow (Molitch & Russell 1990).

Management
The major issues in the management approach to these incidentally detected masses are first to determine whether there is compression of surrounding structures, or the potential for this as might be expected with macroadenomas, and secondly whether there is evidence of hormone secretion from the tumour.

Those patients with evidence of hormone excess should be treated by surgery or with drugs. By our definition, the presence of excess hormonal secretion indicates an incidentally detected, but clinically relevant, tumour that requires definitive management rather than an incidentaloma. Those with a microadenoma and no hormonal abnormalities (true incidentalomas) should have a follow-up scan performed. There is very little evidence on which to suggest guidelines - Reincke suggests rescanning at 1 year with no further studies necessary if there has been no change (Reincke et al. 1990) while Molitch suggests a reasonable approach is to repeat the scan at yearly intervals for 2 years, and if there is no increase in the size of the lesion, to lengthen the interval between scans (Molitch 1995). More data are required, but while the natural history is still unclear, repeat scanning for at least 2 years is preferable.

For non-functioning mesoaenomas and intra-sellar macroadenomas, we suggest MRI, at 6 months and then annually for 2 years in those with no hypopituitarism or visual problems; the data that there are confirm that patients with mesoaenomas and normal pituitary function show no propensity to progress (Reincke et al. 1990). It is uncertain at present for how long this should be continued and more data are clearly needed. Definitive treatment, usually by surgery, should be recommended for those macroadenomas with increased hormone secretion, evidence of hypopituitarism or those with extra-sellar

More data are required to determine the most cost-effective means to follow these patients. Since macroadenomas are the incidentally detected tumours most likely to enlarge, it would appear logical to evaluate these more frequently than incidental microadenomas, as these are much less likely to enlarge in a clinically significant manner. It is debatable, however, whether any macroadenomas should be left and simply monitored, unless they are truly intra-sellar (mesoadenomas). More studies are required before strict guidelines can be produced on duration of follow-up, the frequency of scanning required, and whether predictions can be made, apart from using size, as to which tumours will progress.

Summary
Pituitary adenomas are being detected more commonly because of advances in neuroradiology, the more frequent use of imaging and also progress in biochemical analytical techniques. The label incidentaloma should only be applied after the patient has been assessed for the presence of endocrinopathy or mass effects such as visual field defects. If there is evidence of, for example, hormonal excess, then despite being an incidental finding the tumour is not an incidentaloma as it is clinically relevant and should be treated as any other tumour of that type. True incidentalomas should be followed up with sequential imaging as discussed above to ensure that they are indeed benign and clinically irrelevant.

Suggested management strategy for incidentally detected pituitary tumours
1. Screen for hypo- and hypersecretion of hormones.
2. All extra-sellar macroadenomas require definitive treatment.
3. Tumours associated with syndromes of excess hormone secretion need definitive management.
4. Mass <1 cm diameter - repeat MRI at 1, 2 and 5 years.
5. Mass >1 cm diameter, and intra-sellar - i.e. mesoadenoma - repeat MRI at 6 months, 1, 2 and 5 years.

Adrenal
The detection of incidental adrenal masses has also increased with the improvements in imaging techniques such as ultrasound, CT and MRI. There were 178 reports of adrenal cortical tumours unassociated with excess hormonal secretion as judged by standard biochemical screening prior to 1974 (Lewinsky et al. 1974), and they were described as ‘very rare’ in that paper. In the last two or three decades, however, these incidentally detected tumours have become a common clinical problem, causing them to be described recently as a new epidemic of ‘AIDS’ (adrenal incidentaloma discovered serendipitously) (Griffing 1994). It has also become clear with improved biochemical techniques, that there may be subtle evidence of excess hormone production from these masses previously thought to be non-secretory.

Incidentally detected adrenal lesions provide a similar dilemma to those found in the pituitary gland, although the questions are slightly different - whether the lesion is malignant and secondly whether there is evidence of excess hormonal secretion. These adrenal masses include cortical adenomas secreting steroids, phaeochromocytomas, adrenal carcinomas and metastases, cysts, and myelolipomas as well as non-functioning nodules and adenomas.

Epidemiology
Autopsy studies
There is wide variation in the reported prevalence of adrenal adenomas in autopsy series (Kloos et al. 1995). Adrenal adenomas unassociated with excess hormonal secretion are found in 1-32% of patients in different series (Kloos et al. 1995). This wide range is in part due to the difficulty in distinguishing between cortical nodules, focal hyperplasia and true adenomas. However, if small studies (a total of 50 or less patients) are excluded, the majority of reports show a prevalence of between 1 and 9%, with the two largest studies of 35,000 patients and 9000 patients each reporting a prevalence of 1.97 and 1.45% respectively (Russi & Blumenthal 1945, Russel et al. 1972). Incidentally detected adrenal adenomas occur with equal frequency in males and females, and become more common with increasing age (Kloos et al. 1995). It has been suggested that adrenal nodule formation may be part of the ageing process, and may be secondary to vascular changes (Dobbie 1969).

Imaging
The incidental detection of adrenal masses by CT scanning usually gives a lower prevalence of incidentaloma than the autopsy series, partly due to poor resolution of masses at the smaller end of the spectrum and also because relatively thick scan slices may be used for abdominal imaging (Kloos et al. 1995). CT detects incidental adrenal masses in up to 3.5% of cases depending on the series (Glazer et al. 1982, Abecassis et al. 1985, Beldegrun et al. 1986, Herrera et al. 1991). The reason for the higher frequencies detected in some series is related to whether patients with malignancy were included and whether symptomatic adrenal tumours were included.

CT and MRI are commonly used when screening patients with known malignancy for metastases and the
incidental detection of adrenal masses is commoner in this group of patients. Adrenal metastases have been detected incidentally in 32-73% of cases in various series of oncology patients (Kloos et al. 1995). However, it is important that in those cases where there are no other signs of metastasis an accurate assessment of the adrenal mass is made, as adrenal lesions in patients with known malignancy are not necessarily malignant (Glazer et al. 1982).

Imaging with CT and MRI cannot differentiate the true adrenal incidentaloma from an incidentally detected hypersecretory tumour (Karstaedt et al. 1978, Doppman et al. 1987, Remer et al. 1989, Tsushima 1994). Masses of the adrenal cortex and medulla in asymptomatic patients may subsequently be found to be secretory tumours - e.g. cortisol secreting tumours (Herrera et al. 1991, Reincke et al. 1992) or phaeochromocytomas (Prinz et al. 1982, Herrera et al. 1991, Mannelli et al. 1993, Osella et al. 1994).

Pathology
In over half of cases, incidentally detected adrenal nodules are found to be benign adenomas - both functioning and non-functioning, whilst metastasis to the adrenal gland is the second most common diagnosis in approximately one-third of cases (Cook & Loriaux 1996). Adrenal cysts, phaeochromocytomas, and primary adrenal cancers are all much less common (Table 3).

Cushing’s or subclinical Cushing’s syndrome
It has been clearly demonstrated that Cushing’s syndrome may be found in patients with incidentally detected adrenal tumours and that biochemical evaluation of these cases is important (Reincke et al. 1992, Osella et al. 1994). In addition to the complications of Cushing’s syndrome, unrecognised adenomatous cortisol secretion may lead to a hypoadrenal crisis during surgery to remove the adenoma, due to suppression of cortisol secretion from the contralateral adrenal.

Ross & Aron (1990) suggested using the clinical parameters of obesity and hypertension to screen for this condition in patients with incidental adrenal masses. Most endocrinologists use either an overnight 1 mg or a formal low dose (2 mg/day) dexamethasone suppression test as this is a more accurate screening test (Newell-Price & Grossman 1996), while others suggest using a high dose (8 mg) overnight dexamethasone suppression test since the diagnosis of pituitary dependent Cushing’s syndrome is not a consideration (Chidiac & Aron 1997) (Table 4). It is, however, important to recognise that ACTH dependent Cushing’s syndrome may lead to asymmetrical adrenal enlargement, and give the appearance of a unilateral mass (Cook & Loriaux 1996). Clearly measurement of ACTH and, if detected, a corticotrophin-releasing hormone test are essential in those patients found to have Cushing’s syndrome to determine the underlying cause.

The terms pre-Cushing’s and subclinical Cushing’s syndrome have been used to describe the subset of patients with apparently ‘silent’ adrenal cortical adenomas that possess some features of autonomous function. As the natural history is unclear, we suggest that subclinical rather than pre-Cushing’s is a better term. The cortisol secretion can be sufficient to suppress ACTH, leading to reduced uptake in the contralateral gland on adrenal scintigraphy, and to put the patient at risk of a hypoadrenal crisis. There may be loss of the normal diurnal rhythm of cortisol secretion and dexamethasone suppressibility, despite initially normal cortisol levels (Reincke et al. 1992, Osella et al. 1994). In a series of 122 patients with incidentally detected adrenal masses, 6 (5%) were identified with subclinical Cushing’s syndrome with normal baseline cortisol levels, but loss of the diurnal rhythm of cortisol secretion (McLeod et al. 1990). Three of six patients (50%) had normal 24 h urinary free cortisol but the adrenal scintigraphy showed suppression of the contralateral gland in all cases, illustrating the importance of peri-operative steroid cover to avoid potential Addisonian crisis if adrenalectomy is performed. Further confirmation of the insensitivity of a 24 h urinary free cortisol measurement comes from a study of subclinical Cushing’s syndrome found in 12% of patients with incidentaldomas, where the low dose dexamethasone suppression test was the most helpful screening test (Reincke et al. 1992). Other reports confirm that lack of cortisol suppression with dexamethasone was the most sensitive means of detection of subtle adrenal overactivity in this group (Rosen & Swartz 1992). Six patients out of a series of 45 (14%) with incidentally detected adrenal masses showed loss of the normal circadian rhythm of cortisol secretion, while only 3 had elevated mean serum cortisol levels (Terzolo et al. 1995). There may be a continuous spectrum from non-secretory adenoma to subclinical Cushing’s and full-blown Cushing’s syndrome (Fernández-Real et al. 1994) and this may account for some of the variation in biochemistry.

A large proportion of patients with incidentally detected adrenal tumours have been shown to have low serum dehydroepiandrosterone sulphate (DHEAS) concentrations (Osella et al. 1994, Terzolo et al. 1996). A comparison of 32 patients with incidentally detected adrenal masses and 17 patients with Cushing’s syndrome showed that serum DHEAS levels were lower than normal in 21/24 (87.5%) of the patients with adrenocortical masses (Flecchia et al. 1995). The prevalence of low DHEAS was higher than hormonal alterations suggesting Cushing’s syndrome (17-25% patients) (Flecchia et al. 1995). Suppressed levels may be found where cortisol...
Table 3 | Diagnoses in series of patients with incidentally detected adrenal tumours.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage of series</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s syndrome</td>
<td>0.6% (2/342)</td>
<td>Herrera et al. (1991)</td>
</tr>
<tr>
<td></td>
<td>3.3% (7/210)</td>
<td>Aso &amp; Homma (1992)</td>
</tr>
<tr>
<td></td>
<td>2.2% (1/45)</td>
<td>Osella et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>5.6% (2/36)</td>
<td>Sirén et al. (1993)</td>
</tr>
<tr>
<td>Subclinical Cushing’s syndrome</td>
<td>4.9% (6/122)</td>
<td>McLeod et al. (1990)</td>
</tr>
<tr>
<td></td>
<td>13.3% (6/45)</td>
<td>Osella et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>12% (8.68)</td>
<td>Reincke et al. (1992)</td>
</tr>
<tr>
<td>Mineralocorticoid secreting</td>
<td>3.3% (7/210)</td>
<td>Aso &amp; Homma (1992)</td>
</tr>
<tr>
<td></td>
<td>1.5% (1/68)</td>
<td>Reincke et al. (1992)</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>11% (1/9)</td>
<td>Prinz et al. (1982)</td>
</tr>
<tr>
<td></td>
<td>1.5% (5/342)</td>
<td>Herrera et al. (1991)</td>
</tr>
<tr>
<td></td>
<td>23% (49/210)</td>
<td>Aso &amp; Homma (1992)</td>
</tr>
<tr>
<td></td>
<td>4.4% (2/45)</td>
<td>Osella et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>1.5% (1/68)</td>
<td>Reincke et al. (1992)</td>
</tr>
<tr>
<td></td>
<td>11.1% (4/36)</td>
<td>Sirén et al. (1993)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>1.2% (4/342)</td>
<td>Herrera et al. (1991)</td>
</tr>
<tr>
<td></td>
<td>4.3% (9/210)</td>
<td>Aso &amp; Homma (1992)</td>
</tr>
<tr>
<td></td>
<td>8.8% (4/45)</td>
<td>Osella et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>1.6% (1/63)</td>
<td>Bencsik et al. (1995)</td>
</tr>
<tr>
<td>Metastases</td>
<td>0.8% (1/122)</td>
<td>McLeod et al. (1990)</td>
</tr>
<tr>
<td></td>
<td>0.3% (1/342)</td>
<td>Herrera et al. (1991)</td>
</tr>
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<td>1.4% (3/210)</td>
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<td></td>
<td>2.2% (1/45)</td>
<td>Osella et al. (1994)</td>
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<td></td>
<td>11% (7/63)</td>
<td>Bencsik et al. (1995)</td>
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<tr>
<td>Other</td>
<td>22% cysts (2/9)</td>
<td>Prinz et al. (1982)</td>
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<tr>
<td></td>
<td>11% lipoma (1/9)</td>
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<td></td>
<td>8.6% cyst (18/210)</td>
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</tr>
<tr>
<td></td>
<td>7.1% myelolipoma (15/210)</td>
<td>Aso &amp; Homma (1992)</td>
</tr>
<tr>
<td></td>
<td>2.2% myelolipoma (1/45)</td>
<td>Osella et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>2.2% cyst (1/45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.5% (nodular hyperplasia, haematomas, lipoma, cyst, myelolipoma, adenoma secreting androgens)</td>
<td>Sirén et al. (1993)</td>
</tr>
</tbody>
</table>
secretion from an autonomous adenoma leads to reduced ACTH secretion. In a group of 45 patients with incidentally detected adrenal masses, 42% had DHEAS levels that were significantly lower than those in control subjects (Terzolo et al. 1995). This was the commonest biochemical abnormality. This suggests that subclinical cortisol hypersecretion may be frequently detected in patients with incidental adrenal masses.

Therefore the characteristics of subclinical Cushing’s syndrome may appear to be normal urinary free cortisol levels, absence of typical features of Cushing’s syndrome (although diabetes and hypertension may be associated), absence of cortisol suppression on overnight or low dose dexamethasone suppression testing, loss of the diurnal rhythm of cortisol secretion, suppression of ACTH leading to reduced DHEAS levels and reduced uptake on adrenal scintigraphy, and risk of hypoadrenalism at times of stress.

The crucial question regarding subclinical Cushing’s syndrome is whether this apparently commonly detected condition in patients with incidentally detected adrenal masses has any long-term clinical significance. It would seem unlikely that these tumours will all progress to overt Cushing’s syndrome as this is a very rare diagnosis, whereas these mild degrees of adrenal hypersecretion are common. Secondly, what are the sequelae in terms of risk of osteoporosis in this group? Is this the population who will become hypertensive and diabetic as suggested in some of the earlier studies based mainly on autopsy studies? Is there a risk of hypoadrenalism at times of stress (McCleod et al. 1990)? Interestingly a recent study has demonstrated enhanced bone metabolism in patients with adrenal incidentalomas (Osella et al. 1997). Only when there is more information on the natural history can these questions be answered and so appropriate management advised. Rosen & Swartz (1992) suggested that until these data are available, the insulin tolerance test is the most appropriate test in this group of patients with normal basal cortisol secretion to ensure there is no impairment of the ability to respond to stress. Some suggest surgery as the treatment of choice in patients with subclinical Cushing’s syndrome who have also accelerated hypertension and obesity (Reincke et al. 1992). A limited follow-up study of a small number of patients showed that in those who

### Table 4 Summary of suggestions for investigation of incidentally detected adrenal masses.

<table>
<thead>
<tr>
<th>Hypersecretory state</th>
<th>Screening test/assessment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s or subclinical Cushing’s syndrome</td>
<td>Hypertension, Obesity, 1 mg dexamethasone suppression test, Low-dose (2 mg/day) dexamethasone suppression test and DHEAS</td>
<td>Ross &amp; Aron (1990), Herrera et al. (1991), Kloos et al. (1995), Sirén et al. (1993), Newell-Price &amp; Grossman (1996), Osella et al. (1994), Terzolo et al. (1995)</td>
</tr>
<tr>
<td>Mineralocorticoid hypertension</td>
<td>Blood pressure, Spontaneous hypokalaemia, In hypertensive patients, upright plasma aldosterone and plasma renin activity</td>
<td>Sirén et al. (1993), Ross &amp; Aron (1990), Herrera et al. (1991), Kloos et al. (1995)</td>
</tr>
<tr>
<td>Masculinising tumours</td>
<td>DHEAS, Testosterone and CAH evaluation in virilised females or boys with precocious puberty</td>
<td>Kloos et al. (1995)</td>
</tr>
<tr>
<td>Feminising tumours</td>
<td>Serum oestradiol in feminised men</td>
<td>Kloos et al. (1995)</td>
</tr>
</tbody>
</table>
underwent surgery, there was persistence of abnormal biochemistry in some, while in those who were not operated on, the endocrine abnormalities may persist, appear later or spontaneously remit (Osella et al. 1994).

Aldosterone secreting tumours
Ross & Aron (1990) suggested that screening for spontaneous hypokalaemia is all that is necessary in a hypertensive patient with an adrenal mass, as this produces a negative predictive value of 95% for aldosterone producing adenoma, if the prevalence of hypokalaemia in the general population is assumed to be 10%.

A low sodium diet may mask subtle hypokalaemia in patients with aldosterone secreting tumours, and if the diagnosis is suspected a dietary modification to increase the sodium intake will reduce the false negative rate of this test. Kloos et al. (1995) suggested that in addition to measuring a random serum potassium, patients with hypertension should have paired aldosterone and renin levels checked, while medications are continued. Suspicious results are then interpreted in the light of the drug history and further investigations performed where necessary. There are no data, however, to guide practice in normokalaemic, hypertensive patients, but in those with hypokalaemia investigation is obviously indicated (Table 4).

It is important to recognise that mineralocorticoid hypertension may be due to adrenocortical hyperplasia, and therefore an adenoma may be misinterpreted as an incidentaloma if there is some evidence of nodularity in the other adrenal gland (Reznek & Armstrong 1994). Clearly careful assessment of the renin and aldosterone levels should differentiate these diagnoses in the majority of patients, but adrenal vein sampling may be necessary (Doppman et al. 1992, Sheaves et al. 1996).

Aldosterone producing adenomas may show a significantly lower lipid content on chemical shift MRI (Tsushima 1994); however, the study population in this report was not one of incidentally detected adrenal tumours, and biochemical testing would be more accurate.

Sex hormone producing adenomas
The use of testosterone and oestradiol in screening for incidentally detected adrenal tumours is not recommended due to the rarity of these tumours in truly asymptomatic patients (Kloos et al. 1995). Testosterone should be measured only when indicated, for example in women with virilisation or hirsutism. Oestadiol should be measured in those males with feminisation or gynaecomastia (Copeland 1983).

Congenital adrenal hyperplasia
The diagnosis congenital adrenal hyperplasia (CAH) should be considered in any patient with suggestive clinical features, and appropriate investigations instigated. On the basis of an incidence of a silent adrenal mass in nearly 82% of patients with homozygous and 45% with heterozygous CAH, it has been suggested that CAH should be excluded in all cases of an incidentally detected adrenal mass (Jaresch et al. 1992). The authors suggest that if a mass >6 cm is detected and the patient found to have CAH, then no intervention is necessary as the combination of CAH and adrenal carcinoma is very rare (Jaresch et al. 1992, Ravichandran et al. 1996). A small study comparing the 17-hydroxyprogesterone response to ACTH in patients with adrenal nodules and controls showed that despite similar baseline values, the 30 and 60 min values were significantly elevated over those of the controls (Turton et al. 1992). It is suggested that this may provide a useful test to establish the benign nature of the nodules. Terzolo et al. (1996) showed two distinct groups of steroid secretion in their series of patients with incidentally detected adrenal masses - one group with subclinical Cushing’s and another with an exaggerated response of 17-hydroxyprogesterone to ACTH. However, Reincke (1996) found that two out of four patients with subclinical Cushing’s showed an exaggerated 17-hydroxyprogesterone response. The reason for these discrepant results is unclear and further work is needed.

The exaggerated 17-hydroxyprogesterone response in patients with incidentally detected adenomas has recently been shown to be related to impairment of 11β-hydroxylase rather than 21-hydroxylase activity (Reincke et al. 1997). A controversy does exist, however, regarding the value of screening for CAH and many endocrinologists suggest that no routine biochemical screening is necessary, as adrenal scintigraphy will confirm the presence of a benign lesion (Kloos et al. 1995) (Table 4). If biochemical testing is being performed on the premise that an earlier diagnosis is beneficial, then it may be difficult to justify screening an asymptomatic patient for this condition.

Phaeochromocytoma
The frequency of phaeochromocytoma in a 50 year autopsy series of 40 078 patients from the Mayo clinic was 0.13% (Sutton et al. 1981). In an analysis of appropriate screening tests for incidentally detected adrenal masses, the estimated prevalence of incidentally detected phaeochromocytomas was 6.5% (Ross & Aron 1990). Using the frequency of hypertension and other symptoms in the general population compared with those with phaeochromocytomas, Ross & Aron suggest that the use of hypertension and symptoms will give a negative
and malignant, and these will now be described. Evaluated to assist the accurate distinction between benign and malignant as well as those with benign adenomas, the patients with primary and secondary adrenal tumours, another group found low DHEAS levels in half however, in a series of incidentally detected adrenal masses (Doppman et al. 1991). Serum catecholamines may be used as a screening test, but this test is most useful during a crisis (Bouloux & Fakeeh 1995). It should be noted that there are reports of totally asymptomatic incidentally detected phaeochromocytomas with normal urinary and plasma catecholamines and metabolites, and normal stimulation and suppression tests (Mannelli et al. 1993).

T2 weighted MRI may be helpful in determining whether an adrenal mass is a phaeochromocytoma, as these tumours usually appear hyperintense to the liver (Boland & Lee 1995), although they may sometimes appear iso- or hypointense. A report of T2 weighted MRI studies of 81 adrenal masses, showed that this form of imaging was able to differentiate phaeochromocytomas in all cases from other adrenal masses (Doppman et al. 1987), and therefore MRI is the imaging modality of choice in this situation.

**Adrenal carcinoma and metastases**

The possibility of a neoplasm, either a primary adrenal tumour or a secondary deposit from an extra-adrenal neoplasm, should be considered in every case of an adrenal mass. Primary adrenal carcinomas are often secretory - the prevalence of hormonal secretion varying according to the series and investigations performed. Seventy-five percent of adrenocortical carcinomas in one series were secretory - with cortisol the commonest secretory product (Wooten & King 1993). Endocrinologically active adrenal cancers may also present with evidence of multiple hormone hypersecretion, in contrast to benign adrenal adenomas, which are more usually more specialised in their manifestations. There is controversy over the value of measuring DHEAS. Some suggest DHEAS is a useful test in screening for adrenal carcinoma as it has been shown to be elevated in adrenal carcinoma (Osella et al. 1994); however, in a series of incidentally detected adrenal tumours, another group found low DHEAS levels in half the patients with primary and secondary adrenal malignancy as well as those with benign adenomas, showing that DHEAS was not a useful predictor of hormonal activity (Bencsik et al. 1996).

Various features and investigations have been evaluated to assist the accurate distinction between benign and malignant, and these will now be described.

**Clinical situation**

The clinical situation is rarely helpful when differentiating benign and malignant adrenal masses. There are some instances, however, where taking account of the patient’s presentation can be helpful. For example, non-secretory adrenal masses are likely to be malignant in the presence of an extra-adrenal malignancy but the primary tumour (e.g. bronchial carcinoma) may still be subclinical when the adrenal mass is discovered.

There is also a suggestion that since adrenal malignancy in CAH is very rare, these tumours should not be removed as they are unlikely to be malignant. There are some data to support this. In a study of patients with homozygous or heterozygous CAH, 3/42 had adrenal tumours >6 cm in diameter which were all found to be benign (Jaresch et al. 1992). More data are required in this group.

The majority of cysts, haemorrhages and myelolipomas have characteristic features on CT scanning, and so require no further investigation (Ross & Aron 1990, Korobkin et al. 1996c), although it should be borne in mind that tumours can be partly cystic and may show haemorrhage. The lack of contrast enhancement of cysts compared with the enhancement seen in adenomas may help differentiation in some instances (Reznek & Armstrong 1994).

**Size**

Size is a non-specific and insensitive means of differentiating between benign adrenal lesions and metastases from extra-adrenal primary tumours (Abecassis et al. 1985). In a series of 114 adrenal carcinomas, 105 (92%) tumours measured >6 cm (Copeland 1983). Four patients out of a series of 45 with incidental adrenal tumours were found to have a primary adrenal malignancy - three adrenal carcinomas and one ganglionic neoplasm (Terzolo et al. 1995). A size criterion of 6 cm for surgery in this series would not have missed any adrenal malignancy and included one benign diagnosis of a 7 cm myelolipoma, although the authors recommend using 4 cm as the size criterion for surgery. Using a cut-off of 4 cm, Herrera et al. (1991) reported a ratio of 8:1 benign to malignant, which the authors felt was a reasonable size criterion for surgery, in view of the zero mortality and low morbidity in their operative series. Malignant tumours <2.5 cm are also found (Lee et al. 1991). In a recent survey of 208 patients with incidentally detected adrenal masses, the range in size was 3.2-20 cm and the recommended cut-off for surgery was 4 cm (Karpelik-Zaluska et al. 1997). Using a size of <6 cm in diameter, and absence of CT characteristics suggestive of cancer (irregular borders and inhomogeneity), the negative predictive value for malignancy was calculated to be greater than 99.9% by Ross & Aron (1990). The
positive predictive value of masses 6 cm and larger depends on the actual size and ranges from 35 to 98%, and in view of this Ross & Aron suggest removal of all tumours of >6 cm in diameter. There are many different recommendations on the optimum size cut-off for surgery on suspected adrenal carcinoma - from 3 cm (Thompson & Cheung 1987, Bencskik et al. 1995), to 6 cm (Copeland 1983, Ross & Aron 1990, Sirén et al. 1993). Size can only be used for guidance, and the most widely accepted criterion currently for differentiation between benign and malignant is a diameter >4 cm, with close observation of tumours between 2 and 4 cm in diameter.

**Radiological features**

Certain features on imaging are very suggestive of a sinister lesion - for example increased size, lack of a clearly circumscribed margin and evidence of vascular invasion.

The CT characteristics of adrenal masses that are suggestive of malignancy have been examined, and the measurement of attenuation (as a measure of fat content - higher in benign adenomas) on an unenhanced scan may be better than size criteria in determining malignancy, although there remains a significant overlap (Lee et al. 1991). Different threshold values have been reported from 0 to 18 Hounsfield Units (HU) below which the likely diagnosis is of a benign adenoma (Lee et al. 1991, Van Erkel et al. 1994, Korobkin et al. 1996b). A threshold value of 0 HU had a specificity of 100% for characterisation of benign adrenal masses, with a sensitivity of 47%, whilst a threshold of 10 HU had a sensitivity of 79% and specificity of 96% for benign adrenal tumours (Lee et al. 1991). Korobkin et al. (1996b) reported a significant overlap in size criteria between benign adenomas and non-adenomas, whereas a threshold of 18 HU on the unenhanced CT scan gave a sensitivity of 85% and specificity of 100%. The reason for the discrepancy in thresholds is not entirely clear. A study examining delayed adrenal CT scan 1 h after routine enhanced abdominal CT scan demonstrated that the mean CT scan attenuation value of 41 adrenal adenomas was significantly lower (P<0.001) than 10 adrenal metastases on delayed enhanced CT scan, with very little overlap between the two groups (Korobkin et al. 1996a). Further studies are required to confirm the utility of this technique.

Colour flow Doppler ultrasound does not appear to be helpful in differentiating benign and malignant adrenal masses (Ghiatas et al. 1996).

The use of MRI (Fig. 2) does not require exposure to radiation, but again there is significant overlap between benign and malignant tumour appearance (Reinig et al. 1986, Van Erkel et al. 1994). Dopppman et al. (1987) showed that although T2 weighted MRI scans produce differences between non-functioning adenomas with low signal intensity, and metastases with intermediate intensity, in 20% of cases differentiation was not possible. The tumour/fat signal intensity was found to perform the best of all MRI parameters examined to discriminate adenomas from non-adenomas, although in this study the attenuation values on unenhanced CT was still the best method (Van Erkel et al. 1994). An attempt to improve the accuracy of MRI with an eight echo T2 assessment led to a slight improvement in diagnostic efficacy, but considerable overlap remained (Gruss & Newhouse 1996). Chemical shift MRI has shown promise as a means of differentiating between benign adrenal masses, which typically have a relatively high lipid content, and adrenal metastases (Boland & Lee 1995), with a reported accuracy of 96-100%. More data are needed with this new technique (Fig. 3), particularly as it may not prove to be so promising in the differentiation of primary adrenal carcinoma or phaeochromocytoma from benign lesions (Reinig et al. 1994).

**Fine needle aspiration**

Fine needle aspiration (FNA) has a limited role, enabling a distinction to be made between cystic and solid masses, but usually not allowing differentiation of benign and malignant tumours, as although an increased number of mitoses is suspicious, the diagnosis requires evidence of capsular or vascular invasion (Copeland 1983). Aspiration biopsy should allow the differentiation of metastases from primary adrenal tumours. In a series of 13 patients with an incidentally detected adrenal mass, FNA was performed in 8, and this allowed surgical exploration for diagnostic reasons to be avoided in each case (Gaboardi et al. 1991). The aspiration biopsies showed that two patients with 3 and 4 cm masses had metastatic disease, and that one patient with a 4 cm mass had lymphoma. Silverman et al. (1993), in a retrospective review of 97 patients undergoing 101 image-guided adrenal biopsies, reported the sensitivity of aspiration biopsy as 93% and a negative predictive value (i.e. likelihood that benign histology is accurate) of 100% in masses >3 cm in diameter, whereas in smaller tumours the negative predictive value was only 91% as seven patients with benign FNA had malignancy. This shows that benign histology on biopsy is highly predictive of a benign diagnosis, even in those with known malignancy elsewhere. The complications of the procedure include pneumothorax most commonly (3% in the Silverman series), haemorrhage, bacteraemia and pancreatitis.

**Serial scanning**

The optimal scanning frequency to detect any tumour enlargement in this group of patients is unknown and reflected in the differing protocols suggested - from 3 monthly scans for 1 year and then annually for 2 years.
Turner et al.: Pituitary, adrenal and thyroid incidentalomas

Figure 2 MRI (T2 weighted fast spin echo) showing left adrenal incidentaloma.

Figure 3 MRI in and out of phase gradient echo images demonstrating high fat content of adrenal incidentaloma.
(Abecassis et al. 1985), or repeat scans at 3, 9 and 18 months (Sirén et al. 1993) or serial imaging at 3-6 monthly intervals (Newell-Price & Grossman 1996). The exposure to radiation involved in CT scanning should not be forgotten, and follow-up with MRI is preferable for this reason. A protocol of MRI scanning at 3 months, 6 months and 1 year, with removal of any enlarging mass would seem advisable, with a further scan at 2 years if no enlargement has been detected.

**Adrenal scintigraphy**

Uptake and accumulation of radiotracers such as $[^{131}I]$-6β-iodomethyl norcholesterol, $[^{131}I]$9-iodocholesterol, and $[^{75}Se]$selenomethylnorcholesterol allow localisation of the adrenal gland and of adrenal tumours. Thus functioning tumours such as adrenomas causing glucocorticoid, mineralocorticoid, or androgen excess, and non-hypersecretory adenomas, demonstrate uptake of radioisotope, whilst primary and secondary malignancies will not and appear as ‘cold’ nodules. However, small differentiated malignancies may take up tracer and some cysts or areas of haemorrhage may appear ‘cold’ (Reschini & Peracchi 1984, Pasieka et al. 1992). Negative scintigraphy is unfortunately not so reliable when smaller adrenal masses (i.e. <2 cm in diameter) are examined (Gross et al. 1994). Adrenal scintigraphy may be useful in patients with bilateral adrenal lesions, where absent or reduced uptake compared with the contralateral gland may be considered compatible with a malignancy or destructive lesion (Gross et al. 1995). The significance of a unilateral nodule associated with radioisotope uptake but suppressed contralateral adrenal uptake is likely to be due to suppression of the contralateral gland by hypersecretion from the nodule, although the overnight dexamethasone suppression test and urinary free cortisol may be normal from the nodule, although the overnight dexamethasone suppression test and urinary free cortisol may be normal.

Management is not possible with just one diagnostic test, but a combined effort utilising an endocrinological screening approach, radiological evaluation and radionuclide imaging is required to fully assess these lesions so as not to miss masses with significant pathological potential, but also to avoid unnecessary adrenalectomies.

**Suggested algorithm for diagnosis of incidentally detected adrenal masses**

1. Clinical assessment for symptoms and signs of syndromes of excess hormone secretion, and signs of extra-adrenal primary carcinoma.
2. Short Synacthen test for 17-hydroxyprogesterone (to diagnose CAH) and cortisol (for adrenal insufficiency).
3. If 2 is normal: urinary free cortisol collection and overnight dexamethasone suppression tests; urinary catecholamines; potassium (aldosterone and renin if hypertensive and hypokalaemic) - on 120 mmol/day sodium diet; surgery if syndrome of hormonal excess.
4. If 2 and 3 are normal: surgery if diameter of mass >4 cm, and above results inconclusive of malignancy; if size ≤4 cm and no evidence of hormonal excess or extra-adrenal malignancy, repeat MRI scan at 3, 6, 12 and 24 months.

It is important to recognise that clinical judgement and experience is also required when managing these patients, and in particular which cases should undergo adrenalectomy. The availability of laparoscopic adrenalectomy reduces surgical morbidity (Jacobs et al. 1997).

**Thyroid**

The increasing sensitivity of imaging techniques has led to the incidental detection of thyroid nodules in patients under investigation for other conditions. In a manner similar to incidentally detected pituitary and adrenal masses this has led to a clinical dilemma regarding their clinical relevance and the appropriate management strategy.

**Epidemiology**

The proportion of the general population found to have asymptomatic thyroid nodules depends on the investigation method used - whether it is histological examination of specimens from autopsy or surgical specimens, palpation of asymptomatic patient’s necks or by radiological examination using different imaging techniques (Table 5).

**Histopathological series**

A post-mortem study of 821 thyroid glands from patients who had clinically normal thyroid glands at routine general examination in life showed that 49.5% of the
glands were nodular on visual examination; 12.2% contained a single nodule and 37.3% multiple nodules (Mortensen et al. 1955). Approximately one-third of the patients had nodules >2 cm in diameter. At all ages, nodules were found to be commoner in females, and the frequency increased with age (Mortensen et al. 1955).

**Clinical examination**

Out of a total of 5127 patients recruited from the Framingham cohort, 218 (4.2%) were found to have palpable non-toxic nodules (Vander et al. 1968). The Whickham survey demonstrated thyroid nodules in 0.8% of males and 5.3% of females (Tunbridge et al. 1977). A smaller study found a higher prevalence with 21 (21%) of 100 asymptomatic patients having palpable thyroid nodules - with solitary nodules in 9 and multiple nodules in 12 patients (Ezzat et al. 1994). The reason for the discrepancy between the two studies is not entirely clear, although the smaller study had a larger proportion of women and there was a higher than expected prevalence of positive thyroid microsomal antibodies.

**Imaging**

Several studies have examined the incidence of nodules detected on ultrasound examination of the neck for non-thyroidal conditions (Table 5). This varies according to the population studied, but between 19 and 67% of normal volunteers (Woestyn et al. 1985, Brander et al. 1991, Ezzat et al. 1994) have been shown to have small nodules of <1 cm in diameter. A study of patients undergoing surgery for parathyroid disease demonstrated non-palpable thyroid nodules in 40% using ultrasound and CT (Stark et al. 1983), and duplex ultrasound imaging revealed incidental thyroid nodules 0.6-4.5 cm in size in 13.4% of 67 patients undergoing imaging of the carotids (Carroll 1982). In addition, up to 40% of patients thought clinically to have a solitary nodule actually had multiple nodules detected by ultrasonography (Scheible et al. 1979). The different frequencies with which nodules are detected in these studies reflects the different demographics of the populations studied, differences in the underlying pathology, and the frequency of the transducer (Solbiati et al. 1985).

**Pathology**

Histological examination of thyroid nodules from an autopsy series in subjects with a clinically normal thyroid gland and mean age of 60 years, showed that the commonest finding was a non-neoplastic involutional nodule, present in one-third of all glands and two-thirds of nodular ones (Mortensen et al. 1955). Benign follicular adenomas were found in 27.3% of glands and primary carcinoma in 17/821 (2.1%) thyroid glands. Metastatic carcinoma was detected in 15 (1.8%) glands.

**Natural history**

During follow-up of the Framingham cohort over 15 years, 67 new nodules were detected in the 4909 persons initially free of disease, representing a 15 year incidence rate of 1.7% in females and 0.9% in males, with no evidence of malignancy (Vander et al. 1968). Of the 199 people found to have thyroid nodules at the start of the study, nodules were present and unchanged in 148 patients, and none showed any evidence of malignancy. Forty-five lesions had been surgically removed and all were histologically benign. Further data are required on the malignant potential of incidentally detected or ‘occult’ thyroid nodules.

**Table 5 Epidemiology of incidentally detected thyroid nodules.**

<table>
<thead>
<tr>
<th>Method of detection</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathological (autopsy)</td>
<td>49.5%</td>
<td>Mortensen et al. (1955)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>4.2%</td>
<td>Vander et al. (1968)</td>
</tr>
<tr>
<td></td>
<td>0.8% males and 5.3% females</td>
<td>Tunbridge et al. (1977)</td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>Ezzat et al. (1994)</td>
</tr>
<tr>
<td>Imaging</td>
<td>40% (US and CT)</td>
<td>Stark et al. (1983)</td>
</tr>
<tr>
<td></td>
<td>13.4% (duplex imaging)</td>
<td>Carroll (1982)</td>
</tr>
<tr>
<td></td>
<td>27% (US)</td>
<td>Brander et al. (1991)</td>
</tr>
<tr>
<td></td>
<td>19% (US)</td>
<td>Woesynt et al. (1985)</td>
</tr>
<tr>
<td></td>
<td>67% (US)</td>
<td>Ezzat et al. (1994)</td>
</tr>
</tbody>
</table>

US, ultrasound.
Benign or malignant?

Thyroid carcinoma is relatively uncommon - accounting for approximately 1000 new cases and 300 deaths in England and Wales per year. The main aim when investigating patients with an incidentally detected solitary nodule is to identify the patient with differentiated thyroid carcinoma who requires treatment, while avoiding unnecessary investigations and treatment in the majority. The evidence from epidemiological studies, e.g. the Framingham cohort, suggests that the likelihood of an incidentally detected thyroid nodule being malignant is very low. Furthermore, since occult malignancy may be discovered in up to 2% of thyroid glands that are normal to palpation this may be of little clinical relevance (Mortensen et al. 1995). Others have shown that microcarcinomas may exist in up to 5.7% of adults (Sampson et al. 1974, Fukunaga & Yatani 1975). These occult carcinomas are usually small, <0.5 cm in diameter, papillary in type and show benign behaviour. However, tumours <1 cm in diameter can still metastasise, and can cause death (Boehm et al. 1976). It is not known whether an occult malignancy is a subclinical stage of thyroid malignancy or a tumour whose behaviour is different from thyroid cancers that become clinically relevant. In the future, the genetic characteristics of these tumours may assist with this differentiation.

Certain clinical features should be regarded as highly suspicious of thyroid carcinoma in a patient with an incidentally detected thyroid nodule. These include a nodule discovered in childhood or adolescence (McHenry et al. 1988), or in a male patient (Psarras et al. 1972), or in those with a history of exposure to radiation or a family history of medullary thyroid carcinoma. It has also been suggested that patients from an iodine deficient area may be at a higher risk of thyroid malignancy (Belfiore et al. 1988). Hamming et al. (1990) rated various clinical factors as having high, moderate or low clinical suspicion for thyroid cancer, and showed that patients with one clinical factor with high suspicion for cancer had a 71% incidence of cancer in the nodule, whereas those with a low suspicion had an 11% incidence. Two or more clinical factors with high suspicion led to a 100% chance of cancer. It is interesting that although family history of medullary thyroid carcinoma, rapid tumour growth, very firm nodule, and vocal cord paralysis were all factors shown to be associated with a high suspicion of thyroid carcinoma, age less than 20, male sex, and head and neck irradiation were not shown to have predictive value. Thus it is unlikely that patients with incidentally detected thyroid nodules will have any features that put them in the high suspicion group.

Investigations

The possibility of an incidentally detected nodule causing thyrotoxicosis should be excluded with thyroid function tests. Once this has been excluded, however, the main concern is whether there is a risk that the nodule could be malignant.

Ultrasound

High resolution ultrasonography is very sensitive for the detection of thyroid nodules and often demonstrates multiple nodules in people previously thought to have a single nodule (Brander et al. 1992). Some suggest that since focal abnormalities of the thyroid gland are common, the term ‘nodule’ should be restricted to lesions >5 mm in diameter (Solbiati et al. 1992).

Ultrasonography has not been shown to reliably allow differentiation between benign and malignant nodules (Simeone et al. 1982). Malignant nodules have been reported to be hypoechoic compared with the rest of the gland while benign nodules are hyperechoic with a sonolucent rim or ‘halo’ (Solbiati et al. 1985). However, in one series 7% of cystic lesions were found to be malignant (Ashcraft & van Herle 1981a) and the ‘halo’ sign may also be found in patients with papillary carcinoma (Simeone et al. 1982). Incomplete and irregularly thickened peripheral halo and poorly defined margins are suggestive of malignancy. The distribution of calcification in a nodule gives some clue to the diagnosis - as peripheral calcification is benign, while internal, or punctate calcification within a nodule is suggestive of a papillary carcinoma (Giuffrida & Gharib 1995). Others have demonstrated calcification and cystic changes do not allow complete differentiation between benign and malignant lesions (Woestyn et al. 1985). Thus although ultrasound may accurately define the presence, number and size of nodules, it is not useful for defining the characteristics of the nodule, in particular whether it is benign or malignant.

Radioisotope scanning

Thyroid carcinoma does not usually concentrate radioisotope and therefore will appear ‘cold’ on imaging. However, only 12.8% of cold nodules were malignant, while 6.6% of ‘warm’ nodules were malignant in one study using 131I uptake (Psarras et al. 1972). A review of several studies, which included 4457 patients undergoing radioiodine scans and then undergoing surgery, showed that only 17% of cold nodules were malignant (Ashcraft & van Herle 1981b). Other causes of cold nodules include colloid nodules, cysts or haemorrhage. Hot lesions on radionuclide imaging are rarely associated with malignancy (Freitas et al. 1985), but may represent a hot nodule adjacent to a malignancy.
Therefore, radionuclide imaging cannot distinguish benign from malignant nodules with high specificity. Many feel that the radioisotope scan has no place in the primary distinction between benign and malignant nodules (Giuffrida & Gharib 1995).

FNA cytology
FNA is the most accurate tool presently available for diagnosing malignancy in a thyroid nodule, although it is operator and experience dependent (Ashcraft & van Herle 1981b, Giuffrida and Gharib 1995). There are limitations to the technique as it does not allow assessment of invasion of the capsule or vasculature, and it can be difficult to distinguish follicular adenoma from carcinoma. Those with suspicious histology should therefore be operated on. A recent review of data pooled from seven series of thyroid FNA showed that 69% of nodules were diagnosed as benign, 10% suspicious, 4% malignant and 17% non-diagnostic (Gharib & Goellner 1993). The false negative rates varied from 1.3 to 11.5%, with an average of 5.2%. Unless all patients undergoing FNA have surgery, the true false negative rate will not be known, although most believe this to be less than 5%. The average false positive rate in these studies was 2.9%. It is important to recognise, however, that these are data for palpable thyroid nodules which are not incidentalomas. Löwhagen et al. (1981) suggested that small occult carcinomas are not a target for aspiration biopsy cytology since they are not clinically detectable, and inclusion of these neoplasms may ‘dilute’ the results of pre-operative FNA. There are suggestions that proton magnetic resonance spectroscopy on fine needle aspirates may differentiate benign follicular adenomas from malignant tumours so avoiding the necessity for surgery, but this technique is not widely available (Delbridge et al. 1994). There are few data on the long-term risk of malignancy in incidentally detected thyroid nodules; however, some suggest that those >1.5 cm diameter should have ultrasound directed FNA performed and management depending on the cytology (Giuffrida & Gharib 1995).

Calcitonin
It has been recently suggested that serum calcitonin should be measured in all patients with thyroid nodules (Pacini et al. 1994). Eight out of 1385 (0.57%) patients referred with nodular thyroid disease had elevated calcitonin levels, and had medullary thyroid carcinoma confirmed in all, despite FNA suggestive of medullary thyroid carcinoma in only two of eight patients (Pacini et al. 1994). In a series of 1167 patients with nodular thyroid disease, 504 of whom had solitary nodules, 3% had elevated basal calcitonin levels and medullary thyroid carcinoma was found histologically in 41.1% of these cases, which represented 1.37% of the total series (Niccoli et al. 1997). Further experience is required, particularly in those with incidentally detected thyroid nodules, before screening for medullary thyroid carcinoma is advised in all with nodular disease including incidentally detected nodules.

Management
There are very few data on the natural history of these lesions. Some authors suggest that there is no indication for intervention in these commonly detected abnormalities (Elte et al. 1996). Others feel that those over a certain size should be evaluated further by FNA (Giuffrida & Gharib 1995), while others recommend that those nodules over a certain size should be followed up with clinical assessments. Based on the population data, it seems unlikely that these incidentally detected lesions provide a significant risk of malignancy, and it might be appropriate to suggest investigation only in those with risk factors as mentioned above or clinical features that raise suspicion of malignancy. The investigation of choice should be FNA, which may need to be ultrasound guided where the lesion is small, and management should then proceed as for any solitary nodule. It will be impossible to predict best management, however, until there are more data on the natural history of these lesions, but it appears that thyroid nodules are more likely to be true incidentalomas than adren al or pituitary incidental lesions and unlike the situation in the adrenal gland, and to a certain extent the pituitary, there is no evidence at present that incidentally detecting thyroid lesions is in any way beneficial to the patient in terms of the earlier detection of a significant disease process.

Suggested algorithm for diagnosis of incidentally detected thyroid masses
Diameter <1.5 cm and no risk factors such as irradiation and family history, observe and annual follow-up for 2 years.
Diameter <1.5 cm and risk factors for malignancy - FNA.
Diameter >1.5 cm - FNA.

Conclusions
It is clear that the term incidentaloma is a misnomer when applied in the widest context to serendipitously discovered lesions in the pituitary, adrenal or thyroid gland. Clearly a clinically relevant disorder which requires treatment should not be labelled as an incidentaloma, a term which should be restricted to the detection of a lesion that is associated with no obvious consequence. The pathological and biological significance of true incidentalomas is unknown, but may represent responses to hyperplastic stimuli including the local hormonal and growth factor environment. A better understanding of the genetic
features of incidentally detected lesions may help management in terms of defining which ones may undergo further growth or a change to a more aggressive behaviour pattern. It will be useful to gather further information on conditions such as subclinical Cushing’s syndrome or microscopic carcinoma of the thyroid in order to allow appropriate investigations and management to be instituted. More data are required on the long-term follow-up of these patients, before evidence-based management protocols can be proposed. Although improved imaging techniques have ‘created’ this relatively new dilemma of the ‘incidentaloma’, it is likely that technological developments will help us decide between a true incidentaloma and a subclinical tumour, and to differentiate benign from malignant tumours. However, it is unlikely that these techniques will ever provide 100% diagnostic accuracy for malignancy, and clinical judgement will always be required to assess the data in each individual patient.

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