Selenium-75-cholesterol imaging and computed tomography of the adrenal glands in differentiating the cause of Cushing's syndrome

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Summary
Measurement of \(^{75}\text{Se}\)-cholesterol (Scintadren) uptake and computed tomography (CT) of the adrenal glands were compared as a means of differentiating the cause of Cushing's syndrome in 11 patients over a 2-year period. Quantitative Scintadren imaging differentiated adrenocorticotrophic hormone (ACTH)-dependent disease from local adrenocortical lesions as the cause of Cushing's syndrome in all the patients studied. CT of the adrenal glands rapidly and accurately detected the adrenal mass lesions in 2 cases and was effective in documenting bilateral hyperplasia due to ectopic ACTH-dependent disease. However, in entopic ACTH (pituitary)-dependent disease the adrenal glands were of normal thickness in all but 2 patients, who had bilateral hyperplasia. Scintadren imaging and CT are useful non-invasive procedures for differentiating local adrenal disease from ACTH-dependent disease as the cause of Cushing's syndrome and should be the initial investigations once a firm clinical and biochemical diagnosis of Cushing's syndrome has been made.

The majority of patients with clinically detectable Cushing's syndrome have adrenocorticotrophic hormone (ACTH)-dependent hypercortisolaemia, which may be entopic (pituitary-dependent Cushing's disease) or ectopic, due to extrapituitary production of ACTH and ACTH-related peptides (ectopic ACTH-producing Cushing's syndrome). Between these extremes are patients with Cushing's syndrome due to local adrenocortical lesions (adenoma or carcinoma).

In differentiating the cause of Cushing's syndrome, clinicians have previously relied upon conventional dexamethasone suppression tests, metyrapone administration, administration of synthetic ACTH, and plasma ACTH concentrations, but these tests are arduous and time-consuming. We now report our experience with quantitative adrenal imaging with \(^{75}\text{Se}\)-cholesterol (Scintadren; Radiochemical Centre, Amersham, UK) and computed tomography (CT) of the adrenal glands in elucidating the cause of Cushing's syndrome in 11 patients.

Patients and methods
During the 2-year period August 1980 - September 1982 11 patients with Cushing's syndrome were prospectively evaluated by means of Scintadren imaging and CT of the adrenal glands in an attempt to differentiate the cause of Cushing's syndrome. A firm biochemical diagnosis of Cushing's syndrome had been made on the basis of lack of diurnal variation in plasma cortisol levels, elevation of urinary free cortisol levels and lack of suppression of plasma cortisol levels by low-dose dexamethasone administration (0.5 mg every 6 hours for 48 hours). Scintadren imaging and CT of the adrenal glands have previously been described in detail. Adrenal scintigraphy and calculation of percentage uptake of the administered dose of Scintadren by each adrenal gland were performed 8 days after the intravenous injection of the radiopharmaceutical agent. CT of the adrenal glands was performed on an Elscint 905 whole-body scanner using a slice thickness of 12 mm, a slice increment of 10 mm and a scan speed of 10 seconds. An adrenal gland was considered enlarged if its thickness was > 1 cm.

The cause of Cushing's syndrome was definitively diagnosed by histological study of material and clinical cure after surgery in all except 1 patient who died (case 9). At autopsy the pituitary gland was histologically normal, the adrenal glands were both enlarged with no focal lesions, and the patient was found to be harbouring an undifferentiated large-cell carcinoma at the apex of the right lung, which was presumed to be the ectopic source of the ACTH (further studies on the ACTH content of this tumour are in progress).

Results
Table I depicts Scintadren uptake and CT findings in each of the 11 patients. In the 9 patients with ACTH-dependent Cushing's syndrome Scintadren uptake was bilaterally but unequally elevated, and we presume this to be the result of asymmetrical adrenal hyperplasia with differential hyperfunction of each adrenal gland. CT revealed bilaterally enlarged adrenal glands in the patient with ectopic ACTH-dependent disease, but normal-sized glands in patients with entopic ACTH-dependent disease, except for 2 patients who had bilateral enlargement. In the patient with a unilateral adrenocortical adenoma, Scintadren uptake was high on the side of the adenomatous adrenal gland, while CT identified a 3 cm well-circumscribed lesion of the left adrenal gland, supporting the view that the adenoma was benign; this was confirmed histologically. In the patient with a unilateral adrenocortical carcinoma Scintadren uptake was undetectable, while CT identified a 12 cm lesion of the right adrenal gland with...
an irregular outline which was confluent with the diaphragm. The lesion had necrotic areas in its substance suggestive of malignancy. Surgery confirmed the CT findings and histological examination revealed areas of necrosis and numerous mitotic figures, confirming the malignant nature of this tumour.

The mean Scintadren uptake in patients with ACTH-dependent Cushing’s syndrome was $0.85 \pm 0.23\%$ by the left and $0.99 \pm 0.25\%$ by the right adrenal gland (normal uptake is $0.09-0.25\%$ of the administered dose by each gland).

**Discussion**

Numerous techniques are available for the detection of adrenal lesions. Selective arteriography and venography have been used, but because of their invasive nature (with accompanying complications) and technical difficulty, particularly in catheterizing the right adrenal vein, they are being superseded by simpler non-invasive techniques.

Of the non-invasive techniques, ultrasonography is very much operator-dependent and difficulty is experienced in detecting normal adrenal glands; it would probably not detect hyperplastic adrenal glands but clearly would detect larger adrenal masses. With refinement of technique and availability of more sensitive probes, ultrasound may in the future play a more important role.

Current non-invasive techniques of choice for differentiation of the cause of Cushing’s syndrome are quantitative $^{131}$-cholesterol imaging and CT of the adrenal glands. A $90.6\%$ overall predictive accuracy has been reported with Scintadren in elucidating the type of adrenal lesion in $32$ patients with Cushing’s syndrome. In our series increased Scintadren uptake occurred bilaterally in all $9$ patients with ACTH-dependent disease, while the patient with an adrenocortical adenoma had an elevated Scintadren uptake in the adenomatous gland. Failure to detect any Scintadren uptake in the patient with a carcinomatous adrenal gland is in accord with previous findings in this condition; this is presumably due to the metabolic inefficiency of these tumours in synthesizing adrenal steroids, with contralateral suppression of Scintadren uptake by the normal adrenal gland. This was borne out by the finding of elevated Scintadren uptake by the carcinomatous adrenal gland when imaged again $14$ days after the Scintadren injection. Thus quantitative Scintadren imaging proved highly accurate in differentiating ACTH-dependent Cushing’s syndrome from a local adrenal lesion. However, differentiation of entopic from ectopic ACTH-dependent disease is not possible with this technique.

In a recent study of $37$ patients with biochemically proven Cushing’s syndrome, CT correctly identified all $15$ adrenocortical tumours, distinguishing $5$ carcinomas from $10$ adenomas (carcinomas tended to be irregular or lobulated). Of the $20$ patients with ACTH-dependent hypercortisolaemia, $6$ of the $10$ with Cushing’s syndrome due to ectopic ACTH had bilaterally enlarged adrenal glands while $9$ of $10$ with pituitary-dependent disease had normal-sized adrenal glands. These findings are in accord with ours, where CT correctly identified $2$ adrenocortical tumours and correctly differentiated adenoma from carcinoma. In the patient with the ectopic ACTH syndrome, CT showed bilaterally enlarged adrenal glands, while the adrenal glands were of normal size in all but $2$ of the patients with entopic ACTH disease. Thus CT of the adrenal glands will rapidly and accurately localize adrenal mass lesions and detect ectopic ACTH-dependent disease. The finding of normal-sized adrenal glands on CT would support a diagnosis of Cushing’s disease due to entopic ACTH secretion. This discrepancy in the detection of enlarged adrenal glands by CT in ectopic but not in entopic ACTH disease is borne out by the finding by the pathologist that the adrenal glands were far larger in patients with ectopic ACTH-dependent Cushing’s syndrome.

Scintadren uptake studies and CT complement each other, particularly in entopic ACTH-dependent disease, in which Scintadren uptake is bilaterally elevated but CT of the adrenal glands is usually negative. These findings may be of value in differentiating entopic from ectopic ACTH-dependent Cushing’s syndrome, as by extrapolation bilaterally elevated Scintadren uptake with normal-sized adrenal glands on CT is probably due to entopic ACTH activity.

We propose that quantitative adrenal imaging with Scintadren and CT of the adrenal glands be the initial investigations once a clinical and biochemical diagnosis of Cushing’s syndrome has been made. These procedures will differentiate local adrenocortical lesions from ACTH-dependent Cushing’s syndrome, and differentiate benign from malignant adrenocortical disease. In ACTH-dependent disease, however, it is difficult to differentiate entopic from ectopic disease by these techniques. High bilateral Scintadren uptake with normal-sized adrenal glands on CT would suggest entopic ACTH, while bilateral enlargement of the adrenal glands on CT is more common with ectopic ACTH but does occur with entopic

**TABLE I. SCINTADREN UPTAKE AND CT FINDINGS IN 11 CASES OF CUSHING’S SYNDROME**

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Scintadren uptake (% administered dose)*</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACTH-dependent:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Entopic (pituitary-dependent)</td>
<td>2.3</td>
<td>1.0</td>
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<tr>
<td>2</td>
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<td>0.98</td>
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<tr>
<td>8</td>
<td>Entopic</td>
<td>0.40</td>
<td>1.00</td>
</tr>
<tr>
<td>9</td>
<td>Ectopic</td>
<td>0.88</td>
<td>1.43</td>
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<tr>
<td></td>
<td>ACTH-independent:</td>
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<tr>
<td>10</td>
<td>Adrenal adenoma</td>
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<td>0.17</td>
</tr>
<tr>
<td>11</td>
<td>Adrenal carcinoma</td>
<td>0</td>
<td>0</td>
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</table>

*Normal range for Scintadren uptake is 0.09-0.25% of administered dose by each gland.
Criteria for the diagnosis of pulmonary tuberculosis

B. C. ESCREET, R. L. COWIE

Summary

Diagnostic criteria for pulmonary tuberculosis are presented in the form of a weighted diagnostic protocol. These criteria were evolved to standardize the diagnosis of pulmonary tuberculosis for a prospective study of the disease and its treatment, and were first tested in the evaluation of 469 referred patients, of whom 300 were found to have tuberculosis. The criteria have subsequently been validated clinically and statistically through their application to 1679 patients with radiological abnormalities suggestive of tuberculous disease, of whom 1154 were proved to have pulmonary tuberculosis.

Application of these criteria whenever pulmonary tuberculosis is suspected has removed the dilemma often faced by clinicians when presented with a suggestive chest radiograph, a single sputum smear positive for acid-fast bacilli resembling Mycobacterium tuberculosis, or a strongly positive tuberculin test. We believe that these criteria put each of these separate findings into perspective. They allow the diagnosis of pulmonary tuberculosis to be made with confidence and prevent the erroneous diagnosis of non-tuberculous disease.

Their use should alleviate the tendency towards an overdiagnosis of active pulmonary tuberculous disease, and thereby the waste of therapeutic and social resources.

There is seldom any difficulty in establishing a diagnosis in patients with advanced pulmonary tuberculosis. There are, however, great advantages to the individual patient as well as to the community when pulmonary tuberculosis is diagnosed before the disease has advanced to destroy the lung and to spread the infection to others. Because of this, we have devised and tested a set of diagnostic criteria which allow us to diagnose pulmonary tuberculosis by combining the information gained from the chest radiograph, sputum examination, tuberculin testing and, when necessary, histological examination and the response to a therapeutic trial.

These criteria and the weight which each gives to the diagnostic score have been developed to distinguish active pulmonary tuberculosis from inactive tuberculous lesions of the lung and non-tuberculous lung disease. Allowance has been made for the occurrence of falsely negative and falsely positive bacteriological examination of sputum, as well as for other features which might wrongly cause a diagnosis of pulmonary tuberculosis to be made or rejected.

These criteria have proved to be especially useful in the South African goldmining industry where the diagnosis of pulmonary tuberculosis is usually first suspected after mandatory routine mass miniature radiography.1

REFERENCES