

## Cushing's syndrome

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**During the past 30 years, there have been advances in understanding of the pathogenesis of Cushing's syndrome and in differential diagnosis of its various forms. Improved diagnostic tests and procedures have increased the ability to recognise even mild hypercortisolism and have provided the means to obtain an accurate diagnosis. Despite these advances, the occurrence of unusual clinical presentations and laboratory shortcomings may produce diagnostic problems and challenge clinical intuition. This article reviews recent pathogenic views, new tests, and new diagnostic problems in the evaluation of Cushing's syndrome. Atypical clinical presentations of hypercortisolism and some laboratory shortcomings that may confuse the diagnosis of Cushing's syndrome are also reported.**

Cushing's syndrome is a chronic glucocorticoid excess with various causes. Elucidation of the multiple pathogenetic mechanisms has greatly improved the management of this complex endocrine disorder. However, the syndrome is still associated with substantial morbidity and mortality, and from diagnosis to treatment it represents a challenge for the clinician.

### Pathophysiology

Corticotropin-releasing hormone (CRH), synthesised in the hypothalamus, is the most potent regulator of corticotropin secretion. Corticotropin derives from a larger precursor pro-opiomelanocortin. Proteolysis occurs at pairs of basic aminoacids, generating several peptides, including  $\beta$ -lipoprotein and  $\beta$ -endorphin (the physiological roles of which are unclear) and corticotropin, which specifically stimulates the adrenal cortex.<sup>1</sup> Cortisol, synthesised and secreted by the adrenal cortex, exerts negative feedback on pituitary corticotropin secretion.

The pathogenetic mechanisms of Cushing's syndrome can be divided into those dependent and not dependent on corticotropin (panel 1).<sup>2</sup> The most common form, which is termed Cushing's disease and accounts for 60–80% of cases in most series, is generally due to overproduction of corticotropin from a pituitary adenoma, in most cases a microadenoma (<1 cm in diameter).<sup>3</sup> These tumours are of special interest in elucidation of the process of ontogenesis, because they show only mild abnormalities in comparison with normal corticotrophs. A mutation abnormality might give rise to a group of cells that are resistant to feedback effects and thus are reset to a higher concentration of cortisol in relation to corticotropin.<sup>4</sup> Hyperplasia of pituitary corticotrophs has been described in a minority of patients in whom no tumour could be found.<sup>3,5</sup> Stressful life events have been shown to have a pathogenetic role in hypothalamic-pituitary forms.<sup>6</sup>

Ectopic production of corticotropin may derive from several types of tumours.<sup>7,8</sup> Most patients with ectopic corticotropin syndrome have malignant tumours caused by small-cell lung carcinoma (overt ectopic corticotropin syndrome). Plasma corticotropin concentrations are high in many cases, causing hyperpigmentation. Hypertension, oedema, hypokalaemia, weakness, and glucose intolerance are generally present as manifestations of extremely high cortisol concentrations. The typical Cushing's habitus is not present in many cases, whereas anorexia, weight loss, or other signs of malignant disease are common. Other cases of ectopic production of corticotropin are due to more indolent tumours, such as bronchial, thymic, and pancreatic carcinoids. This form of Cushing's syndrome may mimic pituitary-dependent hypercortisolism and is commonly misdiagnosed and mismanaged (occult ectopic corticotropin syndrome). The major problems arise because some of these tumours secrete amounts of corticotropin and similar compounds overlapping those observed in pituitary-dependent forms.<sup>9</sup> In some cases, the ectopic corticotropin production has characteristics (such as dexamethasone suppressibility or responsiveness to CRH stimulation) typical of Cushing's disease.<sup>10</sup> Moreover, some of these tumours secrete CRH with or without corticotropin,<sup>11</sup> which can confuse diagnostic testing. Most ectopic tumours are benign, and some are so small that they are

#### Panel 1: Causes of hypercortisolism

##### Corticotropin dependent

Pituitary-dependent Cushing's syndrome (Cushing's disease)  
Ectopic corticotropin syndrome (bronchial, thymic, pancreatic carcinoids)  
Ectopic CRH syndrome  
Macronodular adrenal hyperplasia (autonomous)  
Iatrogenic: treatment with corticotropin or its analogues

##### Corticotropin independent

Adrenal adenoma  
Adrenal carcinoma  
Macronodular adrenal hyperplasia  
Micronodular adrenal hyperplasia (including the Carney complex)  
Adrenal hyperplasia caused by abnormal adrenal expression and function of receptors for various hormones (gastric inhibitory polypeptide, vasopressin,  $\beta$ -adrenergic agonists, interleukin 1)

##### Pseudo-Cushing's syndrome

Major depressive disorder  
Alcoholism

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difficult to locate even with sophisticated morphological procedures; but there are also malignant and rapidly progressive cancers.<sup>12</sup>

Forms of autonomous adrenal hyperfunction include adrenocortical adenomas or carcinomas and the rarer primary nodular adrenal hyperplasia. However, the recent identification of several other forms of corticotropin-independent hypercortisolism has further complicated the pathogenesis of Cushing's syndrome (panel 1).<sup>2,13</sup> An intriguing issue is the possibility that adrenal hyperplasia due to chronic stimulation by corticotropin or other factors may evolve towards autonomous nodular adrenal hyperplasia.<sup>14</sup> At variance with this idea, some adrenal nodules decrease in size after removal of the pituitary adenoma, confirming that they are still under corticotropin control.<sup>15</sup> About half the cases of bilateral micronodular hyperplasia, a rare cause of Cushing's syndrome, are in children and in adults younger than 30 years, whereas the other half occur as autosomal dominant disorders. This form, named Carney complex, is a genetic disorder linked to chromosomes 2p16 and 17q2.<sup>16,17</sup>

Adrenal masses discovered by imaging studies for unrelated reasons ('incidentalomas') in the vast majority of cases are non-hyperfunctioning adrenocortical adenomas. Their natural course is still under investigation; however, a minority of such lesions evolve towards overt Cushing's syndrome.<sup>18</sup>

Finally, iatrogenic or factitious Cushing's syndrome may be rarely associated with exogenous administration of corticotropin. Long-term treatment with glucocorticoids (eg, dexamethasone or prednisone) or, in rare cases, with megestrol acetate, may produce clinical features of hypercortisolism.

### Epidemiology

Cushing's syndrome is rare. The estimated annual incidence of pituitary-dependent Cushing's disease is in the range of 0.1 to 1.0 new cases per 100 000,<sup>2,19</sup> and that of Cushing's syndrome (benign and malignant tumours combined) is five to six times less.<sup>2</sup> In most series, including our own (table), Cushing's disease accounts for about 70% of all cases of Cushing's syndrome, with the female to male ratio ranging from three to eight. Ectopic syndrome represents about 12% of cases. Corticotropin-independent causes of Cushing's syndrome include adrenal adenomas (10%) and carcinomas (8%). Such expected prevalence has to be taken into account in assessment of the power of available diagnostic tests. In our patients, age at diagnosis shows a peak in adult women ranging from 25 to 50 years. In children, primary adrenocortical tumours are more frequent than in adults and account for about 30% of cases.

Sign/symptom	Frequency (%)
Truncal obesity	96
Facial fullness	82
Diabetes or glucose intolerance	80
Gonadal dysfunction	74
Hirsutism, acne	72
Hypertension	68
Muscle weakness	64
Skin atrophy and bruising	62
Mood disorders	58
Osteoporosis	38
Oedema	18
Polydipsia, polyuria	10
Fungal infections	6

The mean age of the 239 female and 63 male patients was 38.4 years (SD 13.5; range 8–75).

### Signs and symptoms in our patients (n=302)

### Diagnosis

Cushing's syndrome is characterised by an array of clinical features (table). The occurrence of any single feature ranges so widely among reported series that no single finding is necessary for diagnosis.<sup>19,20</sup> Because clinical manifestations depend on both the degree and the duration of hypercortisolism, diagnostic difficulties arise at onset, when signs and symptoms are generally non-specific. However, certain features, such as weakness associated with proximal muscle wasting, skin atrophy, easy bruising after minor trauma, extensive ecchymoses, purple striae produced by the rapid enlargement of trunk and abdomen, hypertension, and psychological changes, strongly suggest hypercortisolism. On the other hand, some patients present with only isolated symptoms. Even the most common findings, such as truncal obesity and hypertension, may be lacking in some cases.<sup>21</sup> The presence of only a few symptoms common to other disorders may be deceptive, and Cushing's syndrome can be misdiagnosed for a long time and patients treated in rheumatological, psychiatric, or other clinics before the correct diagnosis is achieved. Atypical clinical presentations or forms of pseudo-Cushing's syndrome further complicate the diagnosis. Routine chemistry abnormalities associated with hypercortisolism include neutrophilic leucocytosis, hyperglycaemia, hypokalaemia, hypercholesterolaemia, and hypercoagulable state.<sup>22</sup>

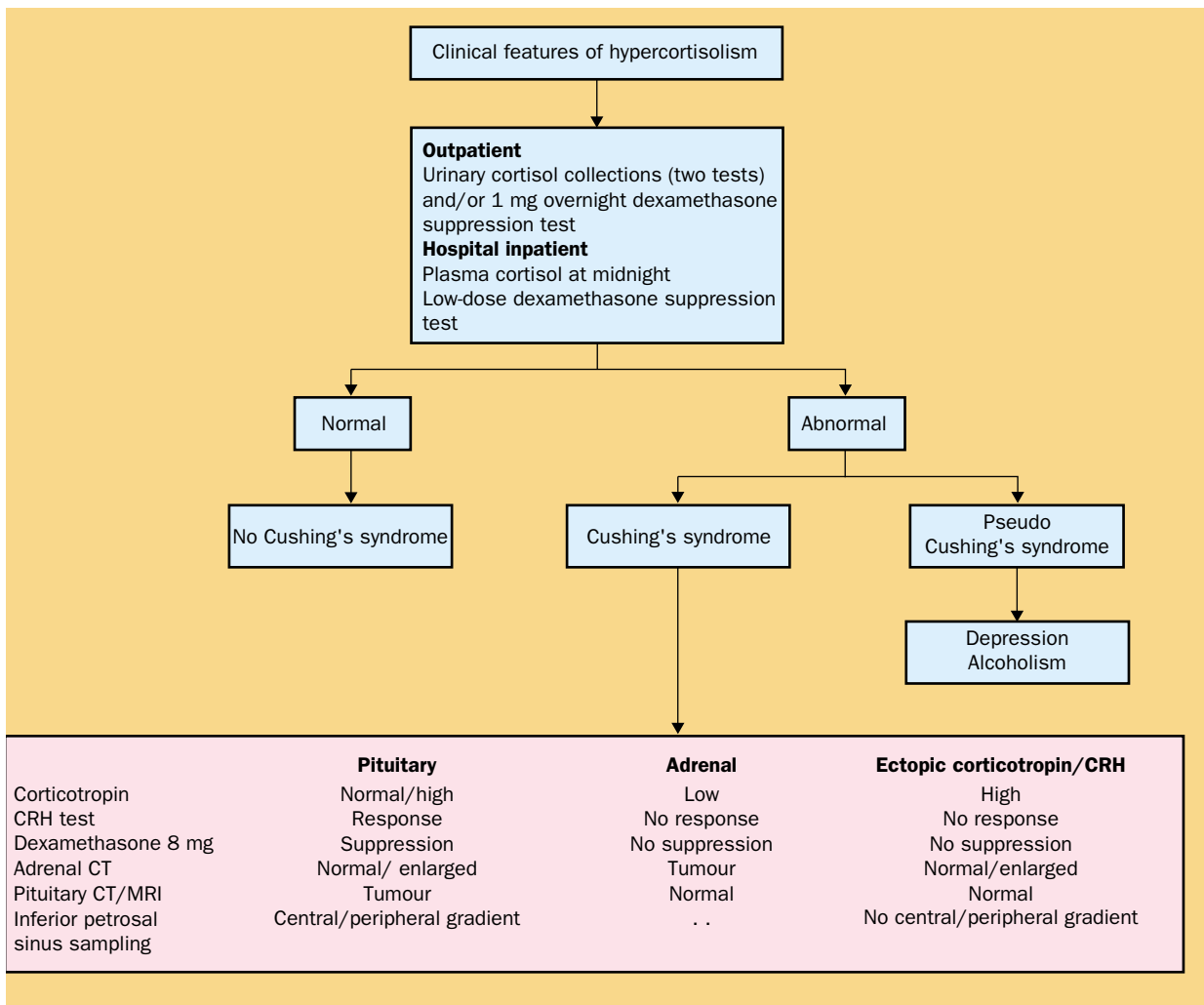
The lack of classic features of hypercortisolism in children may delay the diagnosis and treatment. Because high glucocorticoid concentrations strongly interfere with growth,<sup>23</sup> all children with higher than normal weight and stunted linear growth should be investigated. Various tests proposed in the past three decades have been extensively reviewed, and their diagnostic accuracy discussed in detail.<sup>20,24,25</sup> Both 24 h urinary free cortisol assay and the overnight 1 mg dexamethasone suppression test are suggested for screening of hypercortisolism (figure).

#### Urinary free cortisol

Measurement of urinary free cortisol has the advantages of simplicity and ability to provide an integrated measure of cortisol throughout 24 h.<sup>24</sup> The sensitivity is 95–100% and the specificity 94–98%.<sup>20</sup> Owing to the possibility of inaccurate urine collections and the variability of cortisol secretion from day to day, three 24 h urine specimens collected on an outpatient basis are commonly needed. To assess the adequacy of 24 h collection, creatinine should be also measured, because daily creatinine excretion varies by less than 10% from day to day. Because urinary free cortisol measurements are not valid in patients with renal failure and glomerular filtration rate below 30 mL/min, renal function should be verified before testing.

#### Low-dose dexamethasone suppression tests

In patients with very high urinary free cortisol, these tests add no further useful information. They should be reserved for patients with mild hypercortisolism or suspected pseudo-Cushing's syndrome. The overnight 1 mg dexamethasone suppression test (1 mg at 2300 h or 0000 h) may exclude the presence of Cushing's syndrome when morning concentrations of plasma cortisol are below 50 nmol/L. These strict criteria allow adequate sensitivity (98–100%),<sup>26</sup> although the low specificity limits the test's clinical usefulness. Higher cut-off values can result in a substantial number of false-negative responses, because some patients with mild



### Assessment of Cushing's syndrome

Cushing's disease show unusual sensitivity to dexamethasone suppression. In the 2-day test, a normal response is a morning plasma cortisol concentration below 50 nmol/L after the patient has taken eight doses of 0.5 mg dexamethasone, with intervals of 6 h. This test, which showed sensitivity and specificity of 97–100%,<sup>26</sup> can be carried out in inpatients or outpatients if adequate written instructions are provided. These strict criteria allow exclusion of patients with obesity or pseudo-Cushing's syndrome, but interfering conditions should be considered. There may be no suppression in patients with psychiatric illness, alcoholism, stress, high concentrations of corticosteroid-binding globulin (ie, pregnancy, oestrogen treatment), glucocorticoid resistance, decreased absorption of dexamethasone, those taking drugs that stimulate enzyme activity in the liver (phenobarbital, phenytoin), those presenting with abnormal cortisol metabolism, and those unable to follow directions. False-negative tests can occur in chronic renal failure and in hypothyroidism.

#### Salivary cortisol

Cortisol concentration in saliva is highly correlated with free cortisol in plasma and may distinguish patients with Cushing's syndrome from normal individuals when tested in late evening (at 2300 h) samples. Saliva can be easily collected at home several times to assess cortisol production over long periods.<sup>25</sup>

#### Midnight plasma cortisol

In patients in hospital, a single cortisol measurement on blood taken during sleep at midnight indicates the presence of Cushing's syndrome when values are greater than 50 nmol/L with sensitivity of 100%.<sup>26</sup>

#### New tests

Special tests have been introduced lately to distinguish normal individuals and those with pseudo-Cushing's from patients with mild Cushing's disease. With a 48 h low-dose dexamethasone suppression test followed by CRH stimulation, plasma cortisol remains suppressed in normal people and those with pseudo-Cushing's syndrome (depression and alcoholism) but not in Cushing's disease.<sup>25</sup> Dexamethasone (0.5 mg every 6 h) is administered eight times starting at 1200 h, then CRH (1 µg/kg) is given intravenously at 0800 h (2 h after the last dexamethasone dose). In normal or pseudo-Cushing's individuals, the cortisol concentration does not rise above 39 nmol/L after CRH, whereas it does in those with Cushing's syndrome.<sup>25</sup> Intravenous administration of desmopressin, a drug mainly used to treat central diabetes insipidus, does not consistently increase corticotropin secretion in normal people but it does in patients with pituitary-dependent Cushing's disease. In a recent study,<sup>27</sup> 100% of patients with Cushing's disease responded to desmopressin, so this drug is a promising first-line diagnostic tool. Moreover, the test was useful

also in the postoperative assessment and follow-up of these patients. Despite early interest in this test for differential diagnosis of corticotropin-dependent Cushing's syndrome, there have been reports of ectopic corticotropin-secreting tumours that responded to desmopressin.<sup>25</sup> Newell-Price and co-workers investigated the administration of desmopressin (10 µg) with or without CRH (100 µg).<sup>28</sup> Patients with ectopic corticotropin production responded to the combined test, but the response was significantly lower than in patients with Cushing's disease.

These new tests can give useful information when baseline results are not straightforward.<sup>25</sup> The availability of stable isotopes that allow sophisticated measurement of cortisol production rates by infusion of tracer amounts of cortisol isotopes does not seem to offer any diagnostic advantage.<sup>29</sup>

## Differential diagnosis

### *Corticotropin assay*

Corticotropin measurement represents the first step and the best way to distinguish corticotropin-dependent from corticotropin-independent hypercortisolism. Concentrations below the limit of detection at 0900 h indicate autonomous adrenal hyperfunction. The higher the plasma corticotropin concentration, the more likely is an ectopic source of the hormone, particularly a small-cell lung carcinoma. In active Cushing's disease, plasma corticotropin at 0900 h may be within the normal range, and there may be a significant overlap between concentrations seen with pituitary adenomas and 'occult' ectopic corticotropin-secreting tumours. The immunoradiometric assay, which shows high sensitivity and low detection limits,<sup>30</sup> is widely used but it does not recognise some biologically active variants of corticotropin from ectopic sources. The less specific radioimmunoassay is more effective in measurement of circulating corticotropin-like forms.

### *High-dose dexamethasone suppression test*

Owing to the low sensitivity and specificity of the original criteria for cortisol suppression, new criteria (ie, suppression of urinary free cortisol to less than 10% of baseline for pituitary-dependent Cushing's disease) have been proposed, by which the high-dose dexamethasone suppression test reaches sensitivity of 70% and specificity of 100%. Together with CRH stimulation, this test is the most useful in distinguishing pituitary from ectopic corticotropin-dependent Cushing's syndrome. Suppression with a very high dose of dexamethasone (32 mg in 24 h) has been reported to be more effective, and it has been recommended in 'non-suppressible' pituitary-dependent Cushing's syndrome.<sup>31</sup>

### *CRH stimulation test*

Most pituitary but not ectopic corticotropin-secreting tumours have CRH receptors and show exaggerated corticotropin and cortisol responses to CRH administration. Diagnostic sensitivity and specificity are 93% and 100%, respectively, when the response of corticotropin to CRH stimulation of more than 35% is taken as positive.<sup>32</sup> The largest published series report only the use of ovine CRH, and there have been no large studies with human CRH.<sup>33</sup> Although this test is thought, together with the high-dose dexamethasone suppression test, to be the most useful in diagnosing ectopic corticotropin production, there are cases of ectopic production showing responsiveness to CRH stimulation.<sup>25</sup> Moreover, some of these patients may

respond also to high-dose dexamethasone suppression, leading to a mistaken diagnosis of pituitary-dependent Cushing's disease. CRH testing in combination with other peptides (eg, vasopressin) may represent an improvement over the standard CRH test; however, the data are scanty.<sup>24</sup> Negative results may also be due to mistakes in handling of CRH. The lyophilised peptide easily deteriorates if not carefully diluted immediately before testing.

### *Inferior petrosal sinus sampling*

This approach allows the determination of the site of a corticotropin-secreting lesion (pituitary versus ectopic).<sup>10,25,34</sup> A ratio of central to peripheral corticotropin of more than 2.0, after CRH stimulation, has sensitivity of 95–97% and specificity of 100% in diagnosing pituitary-dependent Cushing's disease.<sup>35</sup> Potential pitfalls of the method are the presence of non-pituitary neoplasms secreting CRH alone or with corticotropin, or very rare disorders such as an ectopic corticotropin-secreting adenoma localised within the sphenoid sinus producing a central to peripheral gradient similar to that of a pituitary-dependent form.<sup>25</sup> This procedure may also help to localise the side of corticotropin-secreting pituitary adenoma. A gradient across left and right sides of greater than 1.4 can predict the exact localisation of corticotropin hypersecretion with accuracy ranging from 5% to 100%.<sup>25</sup> However, an intersinus corticotropin gradient may be lacking in cases of adenoma located in the median wedge of the adenohypophysis and primary diffuse corticotroph cell hyperplasia without adenoma. Moreover, anatomical variability in number and size of anastomotic vessels may also confuse the results.<sup>36</sup> The great variability in results may relate to the expertise of the team doing the test.<sup>37</sup> Although the associated morbidity seems to be low,<sup>38</sup> the test requires experienced teams in specialised centres and should be reserved only for patients in whom diagnostic doubts persist after the more common testing.

## Imaging techniques

Imaging techniques are required for localisation of pituitary or ectopic corticotropin-producing tumours and adrenal masses. Because of their small size, 40–50% of pituitary corticotropin-secreting tumours are not recognised preoperatively despite use of sophisticated methods such as magnetic resonance imaging (MRI) with gadolinium enhancement. By contrast, substantial numbers of the general population have asymptomatic non-secreting microadenomas (pituitary incidentalomas) revealed by MRI.<sup>34</sup> Therefore, morphological localisation of the pituitary tumour is useful only to confirm the diagnosis of Cushing's disease previously made by hormonal testing. At adrenal level, in the majority of patients with corticotropin-dependent Cushing's syndrome, computed tomography (CT) shows bilateral adrenal enlargement, with nodular adrenal hyperplasia in 10–15%, and in up to 30% the adrenal glands are of normal size. In patients in whom an adrenal tumour is suspected, CT or MRI confirms the diagnosis, easily localises the mass, and may help to distinguish benign and malignant forms.<sup>38</sup> Patients with suspected ectopic corticotropin production should be studied by accurate chest and abdominal CT or MRI. Most of these tumours are of neuroendocrine origin and may present with high expression of somatostatin receptors.<sup>12</sup> Advanced scintigraphic methods with radiopharmaceuticals such as indium-111-labelled pentetreotide are able to visualise only tumours bearing sst2 (and sst3 and sst5) somatostatin

receptor subtypes.<sup>39</sup> In the near future, the development of new classes of radiolabelled somatostatin subtype-selective analogues should improve scintigraphic localisation of ectopic corticotropin-secreting tumours. At present, <sup>111</sup>In-pentetreotide scintigraphy could be combined with conventional radiography to improve the accuracy of localisation of these tumours. The radio-labelled cholesterol scintiscan provides morphofunctional information complementary to anatomical imaging and is useful in assessment of malignant disease.<sup>40</sup> Positron-emission tomography has gained clinical acceptance in oncology and can be used to differentiate malignant and benign adrenal masses as well as metastatic lesions<sup>41</sup> and to identify ectopic corticotropin-producing neuroendocrine tumours (unpublished).

### Atypical clinical presentations and rare forms

#### *Intermittent hypercortisolism*

Cortisol hypersecretion with periodicity, varying from a few days to months,<sup>42</sup> may be observed in Cushing's syndrome of pituitary, adrenal, or ectopic origin. Episodes of active hypercortisolism are separated by periods of normal pituitary-adrenal function of varying length as shown by frequent measurements of salivary cortisol in the late evening<sup>25</sup> or tests of urinary free cortisol. For a cost-effective approach, patients can be tested only when they note something wrong, such as swelling, or some clinical signs become apparent.

#### *Adrenal incidentalomas*

1–8% of normal individuals have non-functioning adrenal adenomas, some of which are large enough to be easily recognised by abdominal CT scan. Therefore, a substantial proportion of people who undergo assessment for Cushing's syndrome may be found to have an 'incidentaloma' (ie, an incidentally discovered adrenal mass) that has no relevance to the cortisol overproduction. In these cases, adrenocortical scintigraphy, in addition to hormonal testing, is a useful tool. Bilateral uptake of radiolabelled cholesterol may indicate corticotropin-dependent hypercortisolism, despite the presence of an adrenal mass.<sup>40</sup>

#### *Pigmented micronodular adrenal hyperplasia*

In this disorder, the adrenal glands appear of normal size on CT, but on surgical examination show many small nodular brown or black lesions. Clinical features may include myxomas of the heart, blue naevi, pigmented lentiginosities, endocrine tumours, and peripheral-nerve tumours.<sup>16</sup> Diagnosis may be achieved by a careful clinical examination and, if necessary, by accurate thin-section CT or MRI of the adrenal glands. Some patients show on dexamethasone suppression tests a paradoxical cortisol increase.

#### *Abnormal sensitivity to glucocorticoids*

Clinical and laboratory features of Cushing's syndrome have been reported in rare cases of patients with normal, low, or undetectable cortisol concentrations.<sup>43</sup> The pathophysiology of these forms, due to abnormal sensitivity to glucocorticoid activity or to increased glucocorticoid receptor numbers, is still under investigation. Clinical and laboratory features are similar to those of patients given doses of synthetic glucocorticoids (factitious hypercortisolism).<sup>44</sup> A meticulous search for synthetic glucocorticoids in urine by gas chromatography or by high-performance liquid chromatography may be required in the differential diagnosis.

### Pseudo-Cushing's syndrome

#### *Obesity*

Although not generally accepted as a cause of pseudo-Cushing's syndrome, obesity is the most frequent reason for investigation for Cushing's syndrome. With use of the low-dose dexamethasone suppression and urinary free cortisol tests, Cushing's syndrome can be confidently excluded in the vast majority of patients.

#### *Depression*

Patients with major depression can show some hormonal features of Cushing's syndrome.<sup>45</sup> However, in most cases cortisol hypersecretion is negligible, and only occasional patients in whom severe depression coexists with other symptoms (obesity, hypertension, diabetes) might be mistakenly thought to have Cushing's syndrome with secondary depression.<sup>2</sup> In depressed patients, a cortisol response to insulin-induced hypoglycaemia or lack of response to the low-dose dexamethasone suppression and CRH test may exclude Cushing's syndrome.<sup>20</sup>

#### *Alcoholism*

Alcohol excess can produce in some people clinical features identical to those of Cushing's syndrome.<sup>46</sup> This picture may be associated with abnormalities of cortisol secretion (loss of circadian rhythm). The exact mechanism by which alcohol influences cortisol secretion is still unclear. One hypothesis is that alcohol activates the hypothalamic-pituitary-adrenal axis by increasing the production and secretion of CRH.<sup>46</sup> Normalisation of clinical and hormonal features after ethanol withdrawal is the simplest way to avoid a false diagnosis.

#### *HIV infection*

Pseudo-Cushing's syndrome has been described in HIV-infected patients. This form, in which cortisol concentrations are normal and adequately suppressed by dexamethasone, seems to be due to antiviral therapies.<sup>47</sup>

### Treatment of Cushing's disease

#### *Trans-sphenoidal selective adenectomy*

This operation is the most widely accepted primary therapy for Cushing's disease. Surgical skill and experience are the most important factors for a high success rate. In most centres with special interest in this illness, acceptable results with total remission rates of 80–90% have been achieved for tumours confined to the sella.<sup>2,3,34,48</sup> The criteria for cure should be undetectable plasma cortisol concentration postoperatively. Less strict criteria result in higher rates of apparent cure but higher rates of recurrence. Patients require glucocorticoid-replacement therapy (20–30 mg hydrocortisone daily) from the time of surgery until recovery of the hypothalamic-pituitary-adrenal axis, which is 4–12 months after surgery in most cases. Relapse is defined as recurrence of both clinical and biochemical characteristics of Cushing's syndrome more than 6 months after cure. The main argument for the choice of surgery instead of radiotherapy in recurrences is the possibility of leaving pituitary function intact in most of the cases. However, the results of a second trans-sphenoidal operation in recurrences have been disappointing in most series, with a success rate of 22–64%.<sup>49</sup> Thus, in recurrences, surgical treatment should be considered only for patients with clear morphological signs of pituitary tumour. Use of intraoperative ultrasonography to localise pituitary adenomas in Cushing's disease improved surgical outcome in a recent study.<sup>50</sup> Owing to their hypercoagulable state,<sup>22</sup> patients with Cushing's

syndrome undergoing any type of surgery should receive heparin prophylaxis.

#### *Pituitary irradiation*

For adults not cured by trans-sphenoidal surgery and judged not suitable for a second operation at pituitary level, pituitary irradiation is the most appropriate choice as second-line treatment. In the series of Estrada and colleagues,<sup>51</sup> 83% of patients had remission after radiotherapy. The remissions began 6–60 months after irradiation, but in most cases remission occurred within 2 years of treatment. The only side-effect noted was the development of variable degrees of hypopituitarism in 15 of 30 patients. Radiotherapy, as first treatment, may be used in adult patients in whom high surgical risks or low compliance exclude any surgical approach: remission is obtained in about 55% of these patients.<sup>48</sup> Radiosurgery with the ‘photon knife’ or ‘gamma knife’ in experienced hands implies low risks, but its effectiveness in large series has still to be proved.<sup>52</sup>

#### *Bilateral adrenalectomy*

Bilateral adrenalectomy, which provides the definitive cure in patients for whom cure is not achieved with surgery, radiation, or both, necessitates lifelong continuous monitoring of glucocorticoid and mineralocorticoid replacement therapy. Glucocorticoid replacement is 20–30 mg hydrocortisone daily in most cases. Mineralocorticoid replacement with 9 $\alpha$ -fludrocortisone (50–100  $\mu$ g daily) should be started as soon as intravenous saline is discontinued. Laparoscopic bilateral adrenalectomy may be a valid therapeutic option.<sup>53</sup> However, the benefits must be weighed against the risk of Nelson’s syndrome and other drawbacks. In our experience,<sup>48</sup> about 25% of the patients who underwent bilateral adrenalectomy developed Nelson’s syndrome (dark skin pigmentation, very high corticotropin concentrations, and radiological evidence of pituitary adenoma). Such a proportion is consistent with those reported previously, though rates vary across series and with duration of follow-up.<sup>50,54</sup> Variability may also depend on the criteria for tumour aggressiveness, because there is no consensus definition of Nelson’s syndrome.

#### *Prognostic risk factors*

Survival analysis has been used to assess long-term outcome in Cushing’s disease in multicentre<sup>55</sup> and single-centre<sup>48</sup> studies. In the latter, the estimated cumulative proportion of 79 patients remaining in remission after successful pituitary surgery was 99% after 2 years and 74% after 10 years. Of eight factors examined, statistical significance was found for age, clinical severity, presence of major depression, urinary free cortisol concentrations before and after treatment, and post-treatment corticotropin concentrations. Predictive factors for success of pituitary surgery were also assessed. Surgical failure was significantly associated with the lack of neuroradiological or surgical evidence of pituitary adenoma, a clinical picture noted as severe, and the presence of major depression.<sup>48</sup>

In patients with Cushing’s disease who underwent bilateral adrenalectomy, two risk factors were associated with the occurrence of Nelson’s syndrome: high pretreatment urinary cortisol and the presence of pituitary adenoma. None of our 15 patients without adenoma in the pituitary developed Nelson’s syndrome.<sup>48</sup> Like others, we did not detect a protective effect of pituitary irradiation before bilateral adrenalectomy for

this complication. However, Jenkins and colleagues<sup>56</sup> recommended its use because the frequency of Nelson’s syndrome was lowered by prophylactic pituitary radiotherapy in their sample.

#### *Medical treatment*

Many drugs have been used in the treatment of pituitary-dependent Cushing’s disease (panel 2). They act at hypothalamic-pituitary level and decrease corticotropin secretion, inhibit cortisol synthesis at adrenal level, or compete with cortisol at the receptor level.<sup>57</sup> The neuromodulatory compounds used so far have shown real clinical efficacy only rarely when used as sole treatment, whereas inhibitors of steroid synthesis are effective in most cases in a dose-dependent manner. Through their ability to correct hypercortisolism and its severe complications quickly, they are suitable for critical cases and in preparation for surgery, for patients treated with pituitary irradiation, and whenever a definitive treatment is delayed. Practical guidelines for medical treatment may be summarised as follows.

First, drugs acting at the hypothalamic-pituitary level (serotonin antagonists, dopamine agonists, GABA agonists) are rarely effective. Unfortunately, no predictive criteria for therapeutic outcome can be given, because the response to acute testing may be misleading. A treatment trial of at least 2 weeks with measurements of corticotropin and urinary free cortisol is needed to assess the responsiveness.<sup>57</sup> Bromocriptine, cyproheptadine, sodium valproate, ritanserin, and ketanserin have all been reported to work only occasionally.<sup>58–61</sup>

Second, the most common inhibitors of steroid biosynthesis in clinical use are: mitotane, metyrapone, aminoglutethimide, and ketoconazole (panel 2). The mode of action of mitotane seems to be multifactorial, but the other inhibitors of steroidogenesis that have found most practical clinical application all interfere with reactions catalysed by cytochrome P450. This mechanism of action has little selectivity and extra-adrenal effects are likely.<sup>57</sup> Daily doses should be titrated to maintain urinary cortisol in the normal range, avoiding excessive suppression of adrenal function and the need for glucocorticoid replacement. Patients should be watched for possible adrenal insufficiency and specific toxic effects.

Mitotane has been extensively used in all forms of hypercortisolism. The mechanisms of action involve adrenocorticolytic effects, modifications of steroid peripheral metabolism, and direct inhibition of steroid biosynthesis. Extensive metabolism is required for this drug to be active, and it takes several weeks to reduce

#### **Panel 2: Medical treatment of Cushing’s disease**

##### **Compounds acting at hypothalamic-pituitary level**

Serotonin antagonists (cyproheptadine, metergoline, ketanserin, ritanserin)  
Dopamine agonists (bromocriptine, lisuride)  
GABA agonists (sodium valproate)  
Somatostatin analogues (octreotide)

##### **Compounds acting on adrenal glands**

Mitotane  
Metyrapone  
Aminoglutethimide  
Ketoconazole  
Etomidate  
Trilostane

##### **Compounds acting at receptor level**

Glucocorticoid antagonists (mifepristone)

cortisol secretion. The daily doses currently used for the treatment of Cushing's disease range from 2 g to 4 g, and the monitoring of urinary free cortisol is the best index of response. Replacement therapy requirements are higher than usual, due to interference of hormone-binding proteins.

Metyrapone has been used in the management of various types of Cushing's syndrome.<sup>57</sup> Side-effects due to increased concentrations of androgens (acne, hirsutism) and 11-deoxycorticosterone (hypokalaemia, oedema) as a consequence of 11 $\beta$ /18-hydroxylase inhibition, may be reversed by addition of low doses of aminoglutethimide (a more toxic agent) with predominant inhibition on the cholesterol side-chain cleavage complex.<sup>62</sup>

Ketaconazole is effective as a single agent and at lower doses than the other inhibitors of steroid synthesis. By inhibition of cholesterol side-chain cleavage and 17-hydroxylase/17-20-lyase activities, it can have favourable effects on hirsutism, but its androgenic effects may be disturbing.<sup>63</sup> In most cases, 600–800 mg daily is needed to keep urinary cortisol concentrations within the upper normal limits (to avoid the risk of adrenal insufficiency). According to the effect on adrenal enzymes, a suitable combination would be with low-dose aminoglutethimide, but the association with metyrapone might cause mineralocorticoid hypertension (by accumulation of 11 $\beta$ /18-hydroxylase precursors). By contrast with mitotane, which causes hypercholesterolaemia, ketoconazole interferes with the conversion of lanosterol to cholesterol, leading to low cholesterol concentrations. The occurrence of idiosyncratic hepatotoxic effects may be a limiting factor in its use.<sup>64</sup>

Third, mifepristone is the first potent glucocorticoid antagonist available for clinical use that has affinity for glucocorticoid receptors and very little agonist effect. Only a few patients with Cushing's syndrome have been treated with this drug. Clinical improvement was obtained at high doses (up to 20 mg/kg daily) in forms of hypercortisolism other than pituitary-dependent Cushing's disease. As a result of treatment, cortisol concentrations tend to increase, and therefore monitoring relies only on looking for clinical signs of hypoadrenalism as a marker of overtreatment.<sup>57</sup>

Finally, combined treatments may increase the likelihood of effectiveness.<sup>57</sup> In pituitary-dependent Cushing's disease, there is no treatment strategy valid for all cases. The various therapeutic tools should be selected according to the drug's properties and the particular clinical situation of each patient.

### Treatment of ectopic corticotropin or CRH syndromes

Surgical tumour excision completely cures hypercortisolism, removing the source of ectopic corticotropin or CRH and thereby curing the metabolic disorder. In many patients in whom tumours are not surgically resectable (occult and malignant metastatic), the hypercortisolism can be controlled by inhibitors of steroid biosynthesis. Somatostatin analogues rapidly decrease ectopic corticotropin secretion by some tumours; however, not all ectopic corticotropin-secreting tumours are responsive to this treatment (lack of somatostatin receptors).<sup>57</sup> In patients with severe hypercortisolism due to metastatic malignant tumours or undiagnosed ectopic sources, bilateral adrenalectomy remains the only rational treatment. Laparoscopic bilateral adrenalectomy<sup>65</sup> seems to be a safe and effective procedure, which can be undertaken more easily in

patients with the ectopic corticotropin syndrome, in whom good control of cortisol concentrations is not obtainable with drugs.

### Treatment of primary adrenal hypersecretion

In all cases of autonomous corticotropin-independent Cushing's syndrome, adrenalectomy is necessary (unilateral adrenalectomy in the case of an adrenal adenoma or carcinoma; total bilateral adrenalectomy in the cases of bilateral micronodular or macronodular adrenal hyperplasia). Laparoscopic adrenalectomy has gained wide acceptance as the procedure of choice for resection of most adrenal tumours.<sup>65</sup> The cure rate by surgical removal of adrenal glands is virtually 100%. After unilateral adrenalectomy for an adrenal adenoma, patients need glucocorticoid replacement for several months until hypothalamic-pituitary-adrenal function recovers. After bilateral adrenalectomy, patients need lifelong steroid replacement therapy with both glucocorticoids and mineralocorticoids. Patients with carcinomas almost invariably have progression of disease. In these cases, mitotane alone or in combination with chemotherapy is generally used. This drug, at doses of 2–10 g daily, has been extensively used for the treatment of metastatic adrenocortical carcinoma. Although this drug may offer patients a hope of cure, it is merely palliative in residual or recurrent disease.

### Quality of life

Quality of life in Cushing's syndrome may be seriously compromised even when patients are apparently doing well in hormonal terms during medical management or replacement therapy.<sup>66</sup> Indeed, this endocrine disorder has profound physical and emotional effects, beyond the well-known psychopathology associated with hypercortisolaemic states.<sup>67</sup> Full recovery may be very slow to take place, and help should be provided to overcome as much as possible the neuropsychological (cognitive and emotional) and physical (osteoporosis, hypertension, hypopituitarism) residual impairments. The speed with which psychosomatic recovery occurs may depend on various factors, such as properly individualised glucocorticoid and other hormone replacement (when indicated). Assessment of psychological wellbeing and functional capacity should, therefore, be added to traditional hormonal and clinical variables.<sup>68</sup>

### Conclusion

Cushing's syndrome remains one of the most complex endocrine syndromes. A simplified flow-chart is provided in the figure. The correct assessment of Cushing's syndrome depends on the exact knowledge of its various forms and attention to the pitfalls in the diagnostic evaluation. The choice of tests, the integrity of the specimens, the quality of the measurements, and a close dialogue among clinicians and laboratory are key factors for optimum care of the patients. The treatment of choice is surgery in most cases, in the attempt to eliminate completely the cause of hypercortisolism while minimising the chance of an endocrine deficiency.

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## The uses of error: iatrogenic hepatitis

A 72-year-old woman was admitted to our liver unit with fulminant hepatic failure. She had undergone hip replacement surgery 3 months previously. 2 days after surgery, she developed jaundice and fever with a high rise in transaminases. 7 days later all clinical manifestations resolved. 2 days before admission she underwent a hysterectomy in a private hospital. The day after surgery she became jaundiced, febrile, and developed high transaminases (>1500 U/L) with a low prothrombin time (<20%). A few hours later hepatic encephalopathy developed and she was transferred to our unit. From the notes we detected that during both operations halothane anaesthesia had been administered. The patient worsened and died the next day.

A 58-year-old woman with erythema nodosum, pulmonary adenopathy, and epithelial granulomas on transbronchial biopsy was diagnosed with sarcoidosis. The notes reported a positive Mantoux test one year previously, for which she received isoniazid (300 mg daily) in association with corticosteroid treatment. 3 weeks following initiation of this therapy the patient developed hyperglycaemia, polyuria, and polydypsia. Insulin treatment was initiated. Her liver function tests were normal with the exception of raised transaminases (ALT 261 U/L and AST 116 U/L). Isoniazid was continued at the same dose.

1 month later she developed jaundice, abdominal pain, and severe asthaenia. Serum bilirubin was 22 mg/dL, AST 420 U/L, and ALT 1561 U/L with a prothrombin time of 28%. The patient was admitted to the intensive care unit with the diagnosis of fulminant acute hepatic failure and underwent emergency liver transplantation. All viral serology was negative and she was diagnosed with isoniazid-induced hepatitis. The patient has fully recovered from the liver transplantation.

The clinical histories clearly indicate that these patients developed fulminant hepatic failure following medical errors. An accurate clinical history would have averted repeat halothane anaesthesia in the first case, and adhering to guidelines for preventing antitubercular hepatotoxicity would have prevented liver failure in the second.

As physicians we must accept that our professional activity is of high risk in regard to committing errors and probably all of us have learned more from our errors than from our successes. Diagnostic and therapeutic errors are very common. One of the questions arising from these cases is what attitude we should take towards our colleagues who have erred with such consequences. These questions remain open for debate.

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