

The Approach to the Adult with Newly Diagnosed Adrenal Insufficiency

Wiebke Arlt

Centre for Endocrinology, Diabetes, and Metabolism, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham B15 2TT, United Kingdom

Adrenal insufficiency, primarily presenting as an adrenal crisis, is a life-threatening emergency and requires prompt therapeutic management including fluid resuscitation and stress dose hydrocortisone administration. Primary adrenal insufficiency is most frequently caused by autoimmune adrenalitis, and hypothalamic-pituitary tumors represent the most frequent cause of secondary adrenal insufficiency. However, the exact underlying diagnosis needs to be confirmed by a stepwise diagnostic approach, with an open eye for other differential diagnostic possibilities. Chronic replacement therapy with glucocorticoids and, in primary adrenal insufficiency, mineralocorticoids requires careful monitoring. However, current replacement strategies still require optimization as evidenced by recent studies demonstrating significantly impaired subjective health status and increased mortality in patients with primary and secondary adrenal insufficiency. Future studies will have to explore the potential of dehydroepiandrosterone replacement and modified delayed-release hydrocortisone to improve the prospects of patients with adrenal insufficiency. (*J Clin Endocrinol Metab* 94: 1059–1067, 2009)

The Case

A 20-yr-old man is referred to the acute admissions unit because of severe weakness and postural hypotension, progressively worsening over the last 3 months. Two months ago he had sought the advice of his general practitioner because of fever, fatigue, lack of energy, and dizziness. A provisional diagnosis of a viral infection had been established, and symptoms had temporarily improved after several days of saline infusion. His previous medical history is unremarkable. He is slightly underweight (body mass index, 19.1 kg/m²), having lost 8 kg over the last 3 months despite good appetite. Inspection reveals significant dehydration and generalized dark pigmentation of the skin. The latter has been present for the last 3 yr, described by the patient as “a suntan all year round for free.” Closer examination reveals hyperpigmentation of the palmar creases and the knuckles and patchy hyperpigmentation of the oral mucosa. His supine blood pressure is 70/40 mm Hg, his heart rate is 130 beats per minute, and he is not able to sit up because of dizziness. His full blood counts show normocytic anemia (hemoglobin, 11.0 g/dl; normal, 14–18), biochemistry results reveal low sodium (127 mmol/liter; normal, 135–149), high potassium (5.4 mmol/liter; normal, 3.5–5.0), and slightly increased creatinine (160 μmol/

liter; normal, 50–101). Adrenal function test results are as follows: baseline cortisol below 20 nmol/liter, increasing to 31 nmol/liter 30 min after cosyntropin 250 μg iv; baseline plasma ACTH above 1250 pg/ml (normal, 9–56). His thyroid function test results are as follows: TSH below 0.01 mU/liter (normal, 0.4–4.1), and free T₄, 79.9 pmol/liter (normal, 10.0–24.6).

Background

This young man suffers from adrenal insufficiency as proven by insufficient cortisol production with baseline levels below the limit of detection and failure to produce a peak cortisol above 500 nmol/liter 30 min after cosyntropin administration. Concurrently, pituitary ACTH secretion is in overdrive, indicative of primary, *i.e.* adrenal origin of disease. The prevalence of Addison’s disease, mostly due to autoimmune adrenalitis, is 93–140 per million, whereas secondary insufficiency, mostly due to hypothalamic-pituitary tumors, has a prevalence of 125–280 per million (1). The overall prevalence of adrenal insufficiency is 5 in 10,000 population, with three patients suffering from secondary adrenal insufficiency, one from primary adrenal insufficiency due to autoimmune adrenalitis, and one from congenital adrenal

hyperplasia. However, the latter plays no significant role in newly diagnosed adrenal insufficiency in adulthood because classic congenital adrenal hyperplasia usually manifests neonatally or in early childhood and its nonclassic variant only very rarely results in an initial presentation with adrenal crisis. This paper will focus on the diagnostic evaluation and therapeutic management of newly diagnosed adrenal insufficiency in the adult patient. Adrenal insufficiency in children due to other causes than congenital adrenal hyperplasia is a rare event and requires a more complex differential diagnostic and distinct therapeutic approach (2).

Clinical Considerations

Presentation with acute adrenal insufficiency, *i.e.* life-threatening adrenal crisis, as in our patient, requires an immediate, combined diagnostic and therapeutic approach. Hemodynamically stable patients may undergo a cosyntropin stimulation test; if in doubt, baseline bloods for serum cortisol and plasma ACTH will suffice, and if cortisol is below 100 nmol/liter while ACTH is considerably elevated, there is no doubt about the diagnosis. Formal confirmation of diagnosis can be performed after clinical improvement. Diagnostic measures must never delay treatment, which should be initiated upon strong clinical suspicion of adrenal insufficiency. It is of negligible risk to start hydrocortisone and stop it after adrenal insufficiency has been safely excluded; withholding potentially life-saving treatment, however, could have fatal consequences. Our patient certainly needs immediate therapeutic attention, with signs and symptoms very suggestive of adrenal insufficiency, including patchy hyperpigmentation of the oral mucosa and the presence of severe hypovolemic hypotension. With his peripheral veins collapsed, he actually required a central line for iv fluid resuscitation at an initial rate of 1 liter/h and continuous cardiac monitoring. In addition, he was commenced on hydrocortisone by iv injection of 100 mg hydrocortisone followed by continuous infusion of 150 mg hydrocortisone in 5% glucose per 24 h. Mineralocorticoid replacement does not need to be added in the acute setting as long as the total daily hydrocortisone dose is greater than 50 mg because such a dose will ensure sufficient mineralocorticoid receptor activation by cortisol (Table 1).

Diagnostic Evaluation

Adrenal insufficiency is readily diagnosed by the cosyntropin test, a safe and reliable diagnostic tool with excellent long-term predictive value (3, 4); it is important to be aware of the considerable variability between results of different cortisol assays (5), and when defining the cutoff for failure, commonly set at 500 nmol/liter, one should ideally refer to results from a local reference cohort obtained with the same assay. The diagnostic value of the cosyntropin test is only compromised within the first 4 wk after a pituitary insult (4, 6) because during this period the adrenals will still respond to exogenous ACTH stimulation despite the loss of endogenous ACTH drive. When suspecting secondary

adrenal insufficiency, the insulin tolerance test is an alternative choice for diagnostic confirmation, considered by many as the gold standard, however associated with side effects and requiring exclusion of cardiovascular disease and history of seizures. Formal confirmation of diagnosis by the cosyntropin stimulation test should include blood samples for plasma ACTH, which will guide the way for further diagnostic assessment by reliably differentiating primary from secondary adrenal insufficiency, *i.e.* adrenal from hypothalamic-pituitary disease (Fig. 1).

In our patient, glucocorticoid deficiency is confirmed not only by the lack of response to cosyntropin stimulation but also by baseline cortisol below the limit of detection. Possible glucocorticoid deficiency is also indicated by his normocytic anemia because sufficient levels of cortisol are required for maturation of blood progenitor cells; other blood count changes may include lymphocytosis and eosinophilia. Sometimes mild metabolic acidosis or hypercalcemia can also be observed in patients, the latter mostly in the context of coincident hyperthyroidism. Serum glucose may be low; however, significant hypoglycemia as a presenting sign plays a more important role in childhood adrenal insufficiency where it can result in significant brain damage. However, in a patient with preexisting type 1 diabetes, onset of recurrent hypoglycemic episodes despite unchanged insulin regimen should raise the suspicion of adrenal insufficiency.

Mineralocorticoid deficiency is present in primary adrenal insufficiency only; the renin-angiotension-aldosterone system in patients with hypothalamic-pituitary disease and intact adrenals is usually preserved. In our patient, not only is mineralocorticoid deficiency reflected by the arterial hypotension and deranged potassium and sodium, but intravascular volume depletion is also indicated by the slightly raised creatinine, a common finding in Addison patients. Hyponatremia is observed in about 80% of acute cases whereas less than half present with hyperkalemia.

Adrenal androgen deficiency can be present in both primary and secondary adrenal insufficiency. Characteristically, serum dehydroepiandrosterone (DHEA) sulfate (DHEAS) will be low or undetectable in adrenal insufficiency, which however only bears diagnostic value in patients younger than 40 yr due to the age-associated decline in adrenal DHEAS secretion. DHEA is a crucial precursor of adrenal androgen synthesis, and the majority of androgens in females originate from adrenal DHEA production (7); therefore females with adrenal insufficiency will report loss of pubic and axillary hair, and also dry and itchy skin and loss of libido.

In our patient, primary adrenal insufficiency is confirmed by very high ACTH levels, also reflected by hyperpigmentation in areas of increased shear stress to the skin. In addition, his thyroid function test results revealed overt hyperthyroidism, thus making a *prima facie* case for autoimmune polyglandular syndrome (APS) as the underlying diagnosis. In North American and European countries, autoimmune adrenalitis accounts for more than 90% of cases with primary adrenal insufficiency; in 40%, adrenal insufficiency is isolated, whereas in 60% it arises as part of an APS (1, 8). APS type 1, also termed autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, accounts for 15% of cases and is characterized by adrenal insufficiency, hypoparathyroidism, and chronic mucocutaneous candidiasis, the

TABLE 1. Recommended therapeutic approach to adrenal insufficiency

Acute adrenal insufficiency	
Glucocorticoid replacement	Start on physiological saline infusions, initial rate 1 liter/h under continuous cardiac monitoring conditions Administer 100 mg hydrocortisone as an iv injection, followed by 100–200 mg hydrocortisone in glucose 5% per continuous iv infusion (alternatively, administer hydrocortisone im at a dose of 25–50 mg four times daily)
Mineralocorticoid replacement	Only in primary adrenal insufficiency Not required as long as hydrocortisone dose >50 mg per 24 h
Adrenal androgen replacement	Not required
Chronic adrenal insufficiency	
Glucocorticoid replacement	Primary adrenal insufficiency: start on 20–25 mg hydrocortisone per 24 h Secondary adrenal insufficiency: 15–20 mg hydrocortisone per 24 h; if borderline fail in cosyntropin test consider 10 mg or stress dose cover only Administer in two to three divided doses with two thirds and half of the dose, respectively, administered immediately after waking up Monitoring: <ul style="list-style-type: none"> • Check body weight, calculate body mass index • Check for signs of underreplacement (weight loss, fatigue, nausea, myalgia, lack of energy) • Check for signs of overreplacement (weight gain, central obesity, stretch marks, osteopenia/osteoporosis, impaired glucose tolerance, hypertension) • Take a detailed account of stress-related glucocorticoid dose self-adjustments since last visit, potential adverse events including emergency treatment and/or hospitalization
Mineralocorticoid replacement	Only required in primary adrenal insufficiency Not required as long as hydrocortisone dose >50 mg per 24 h Start on 100 µg fludrocortisone (doses vary between 50–250 µg per 24 h) administered as a single dose in the morning immediately after waking up Monitoring: <ul style="list-style-type: none"> • Blood pressure sitting and erect (postural drop ≥20 mm Hg indicative of underreplacement, high blood pressure may indicate overreplacement) • Check for peripheral edema (indicative of overreplacement) • Check serum sodium and potassium • Check plasma renin activity (at least every 2–3 yr, upon clinical suspicion of over- and underreplacement and after significant changes in the hydrocortisone dose (40 mg hydrocortisone = 100 µg fludrocortisone)
Adrenal androgen replacement	Consider in patients with impaired well-being and mood despite apparently optimized glucocorticoid and mineralocorticoid replacement and in women with symptoms and signs of androgen deficiency (dry, itchy skin; reduced libido) DHEA 25–50 mg as a single morning dose; in women also consider using transdermal testosterone (300 µg/d, i.e. two patches per week) Monitoring: <ul style="list-style-type: none"> • In women, serum testosterone and SHBG (to calculate free androgen index) • In men and women on DHEA replacement, serum DHEAS and androstenedione levels • Blood should be sampled at steady state, i.e. 12–24 h after the last preceding DHEA dose
Additional monitoring requirements	Regular follow-up in specialist center every 6 to 12 months In primary adrenal insufficiency of autoimmune origin (isolated Addison or APS) Serum TSH every 12 months In female patients: check regularity of menstrual cycle, consider measurement of ovarian autoantibodies if family planning not finalized Check emergency bracelet/steroid card, update as required Check knowledge of “sick day rules” and reinforce emergency guidelines involving partner/family members Consider prescription of a hydrocortisone emergency self-injection kit, in particular if delayed access to acute medical care is likely (rural areas, travel) Check if other medication includes drugs known to induce (e.g. rifampicin, mitotane, anticonvulsants such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital, topiramate) or inhibit (e.g. anti-retroviral agents) hepatic cortisol inactivation by CYP3A4, which may require glucocorticoid dose adjustment

latter being the primary manifestation in most cases and already apparent in childhood (9). APS1 is caused by mutations in the autoimmune regulator gene *AIRE* (10–12), whereas APS type 2 is thought to be inherited as a complex trait, associated with loci within the major histocompatibility complex (8) and distinct susceptibility genes (13–15). APS2 is much more common than APS1 and in addition to adrenal insufficiency most frequently comprises autoimmune thyroid disease, albeit more often autoimmune hypothyroidism than Graves’ disease as in our patient. It is important to recognize that cortisol exerts inhibitory control

on TSH secretion (16); thus, mild to moderately elevated TSH levels up to 10 mU/liter are frequently observed in acute adrenal insufficiency. This cannot be considered as proof of coexisting autoimmune hypothyroidism (17) and typically, in the absence of autoimmune thyroid disease, TSH normalizes after implementation of glucocorticoid replacement therapy. As a guide, one should refrain from initiating T₄ replacement therapy in the setting of acute adrenal insufficiency because an increase in T₄ levels will speed up cortisol breakdown and thereby might aggravate signs and symptoms of hypocortisolism.

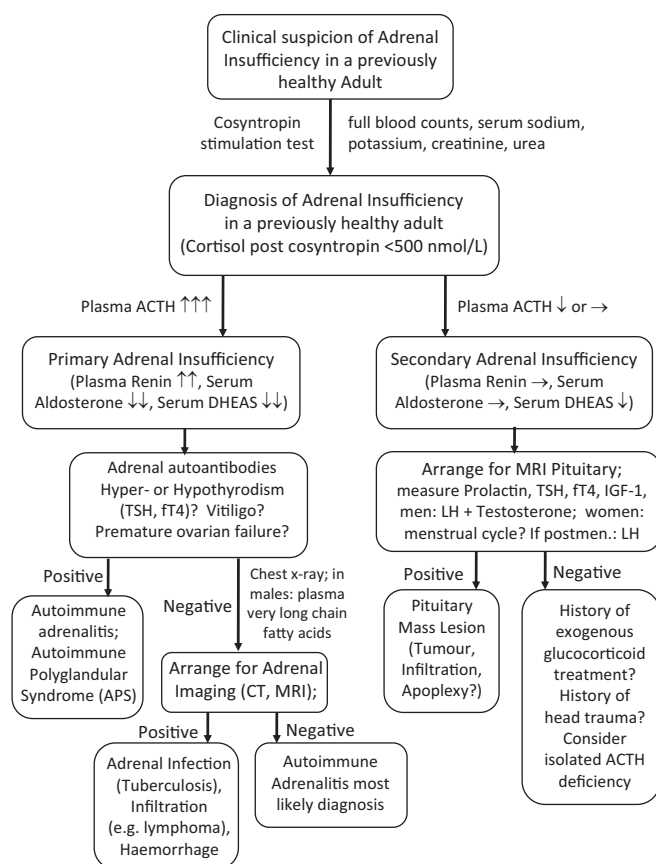


FIG. 1. Flowchart outlining the steps to be taken for the diagnostic management of adults with newly diagnosed adrenal insufficiency. CT, Computed tomography; fT4, free T₄.

Autoantibody screening in our patient showed negative adrenal autoantibodies but positive thyroid autoantibodies. This is entirely consistent with his history of long-standing hyperpigmentation, indicating that his adrenal insufficiency started to develop several years ago. By contrast, his current, acute presentation was most likely caused by the recent onset of hyperthyroidism, a metabolic situation resulting in not only increased demand for cortisol but also increased clearance of residual circulating cortisol (18). He could have presented with adrenal crisis any time after intercurrent illness or trauma, *i.e.* situations of significant stress that his failing adrenals would have been unlikely to cope with.

If there is no coexisting autoimmune disease and adrenal and steroid autoantibodies are negative, imaging of the adrenals, preferably by computed tomography, is warranted (Fig. 1). Tuberculosis should be considered, which is seen frequently in developing countries and therefore also in migrant populations. Chest x-ray is helpful, and imaging of the adrenals typically shows hyperplastic organs in the early phase and spotty calcifications in the late phase of tuberculous adrenalitis. Much rarer causes are bilateral infiltration by bilateral primary adrenal lymphoma (predominantly lung cancer), metastases (19, 20), sarcoidosis, hemochromatosis, or amyloidosis. Bilateral adrenal hemorrhage is usually only seen during septic shock or in very rare instances in primary antiphospholipid syndrome (21). In male patients with isolated Addison's and negative autoantibod-

ies, imaging should be preceded by measurement of plasma very long chain fatty acids to safely exclude X-linked adrenoleukodystrophy that affects 1 in 20,000 males (22). *ABCD1* gene mutations encoding for the peroxisomal adrenoleukodystrophy protein involved in cross-membrane transport manifest in 50% of cases in early childhood and primarily with central nervous system symptoms. However, the adrenomyeloneuropathy variant accounting for 35% of cases can manifest with adrenal insufficiency before the development of spinal paraparesis during early adulthood (22).

If ACTH is inappropriately low in the presence of cortisol deficiency, imaging of the hypothalamic-pituitary region by magnetic resonance imaging (MRI) is the first diagnostic measure that should be arranged for, alongside an endocrine pituitary baseline profile (Fig. 1). Pituitary adenomas are most common; craniopharyngiomas are much rarer and may present at any age; very rare causes include meningioma, metastases and infiltration by sarcoidosis, Langerhans cell histiocytosis, or other granulomatous disease. Careful history taking should ask for previous head trauma (23, 24), surgery, radiotherapy, and clinical indicators of pituitary apoplexy (25), *i.e.* the sudden onset of high impact headache (26). The latter may occur spontaneously in larger pituitary adenomas or may result from sudden hypocirculation during surgery or as a consequence of complicated deliveries with significant blood loss, the classical cause of Sheehan's syndrome. Lymphocytic hypophysitis of autoimmune origin (27) commonly presents with panhypopituitarism including diabetes insipidus and a pituitary mass effect. However, it may present with isolated ACTH deficiency, in some cases coinciding with autoimmune thyroid disease (28, 29).

Importantly, the most obvious cause should not be forgotten: suppression of the hypothalamic-pituitary axis by exogenous glucocorticoid treatment. This should always be excluded, considering not only oral steroid intake but also glucocorticoid inhalers, creams, or intraarticular injections.

Treatment

Glucocorticoid replacement

Physiological daily cortisol production rates vary between 5 and 10 mg/m² (30), which is equivalent to the oral administration of 15 to 25 mg hydrocortisone, *i.e.* cortisol. After oral ingestion, cortisol produces highly variable peak concentrations within the supraphysiological range followed by a rapid decline to less than 100 nmol/liter 5 to 7 h after ingestion. I usually recommend the administration of hydrocortisone in two to three divided doses, *e.g.* 15 mg in the morning upon awakening, followed by 5 mg 6 h later, or 10 mg upon awakening followed by 5 mg 4 h and 8 h later, respectively. It is important to let the patient experiment with different timings to find the most suitable regimen for his individual needs. Importantly, patients who work shifts have to adjust the timing of the glucocorticoid doses to their working times and subsequent sleep-wake cycle. Whether a thrice daily glucocorticoid regimen should be preferred over twice daily administration is not clear because well-designed and appropriately powered studies are lacking. Some

groups advocate weight-related dosing (31), and this appears to generate a smoother pharmacokinetic profile, but data demonstrating superiority of such a regimen are lacking. However, body surface area-adjusted glucocorticoid dosing is commonly used for guiding glucocorticoid replacement in children.

When deciding on the glucocorticoid dose, it is important to consider concurrent medication, in particular drugs known to increase hepatic glucocorticoid metabolism by CYP3A4 induction, which results in increased 6 β -hydroxylation and hence cortisol inactivation. A multitude of drugs are known to induce CYP3A4 (Table 1), which require a 2- to 3-fold increase in glucocorticoid dose. Conversely, the intake of drugs inhibiting CYP3A4 (Table 1) would require reduction of glucocorticoid replacement dose. Overt hyperthyroidism will also increase hydrocortisone metabolism. Therefore, the initiation of glucocorticoid replacement in patients with newly diagnosed hypopituitarism should always precede the initiation of T₄ replacement because the reverse might precipitate adrenal crisis. Pregnancy is associated with a gradual increase in cortisol-binding globulin and thus total cortisol. However, during the last term free cortisol increases, which requires a 30–50% increase in hydrocortisone dose.

The oral administration of currently available cortisol preparations is not able to mimic the physiological pattern of cortisol secretion, which follows a distinct circadian rhythm. Cortisol secretion begins to rise between 0200 and 0400 h, peaks within 1 h of waking, and then declines gradually to low levels during the evening and nadir levels at and after midnight (32). There is evidence for a diurnal variability in glucocorticoid sensitivity. Plat *et al.* (33) have demonstrated a more unfavorable metabolic response to evening administration of hydrocortisone. Also, high levels of glucocorticoids may disrupt sleep, and thus late evening hydrocortisone administration should be avoided; sleep disturbances contributing to increased fatigue are a common feature in chronic adrenal insufficiency (34, 35). The delivery of cortisol by iv infusion (36) or sc pump (37) can closely mirror diurnal secretion, but these administration modes are obviously not suited for routine delivery. Recently developed modified- and delayed-release hydrocortisone preparations mimicking physiological cortisol secretion represent a very promising therapeutic approach (38, 39).

Cortisone acetate requires intrahepatic activation to cortisol by 11 β -hydroxysteroid dehydrogenase type 1, which contributes to a higher pharmacokinetic variability compared with hydrocortisone; 25 mg cortisone acetate is equivalent to 15 mg hydrocortisone (18, 40). Long-acting glucocorticoids are also used for replacement, *e.g.* in 20% of respondents to the 2002 survey of the North American Addison Disease Foundation. Some countries do not have access to hydrocortisone or cortisone acetate and therefore have to resort to long-acting synthetic glucocorticoids. However, prednisolone and dexamethasone have considerably longer biological half-lives, likely resulting in unfavorably high night-time glucocorticoid activity with potentially detrimental effects on insulin sensitivity and bone mineral density (41). In addition, available preparations offer limited options for dose titration. Therefore I generally recommend against the use of synthetic glucocorticoids for replacement therapy in adrenal in-

sufficiency; the only exception are patients with concurrent insulin-dependent diabetes in whom prednisolone may help to avoid the peaks and troughs of hydrocortisone pharmacokinetics and thus also subsequent rapid changes in glucose control. For clinical purposes, I assume equipotency to 1 mg hydrocortisone for 1.6 mg cortisone acetate, 0.2 mg prednisolone, 0.25 mg prednisone, and 0.025 mg dexamethasone, respectively. Although equipotency doses of hydrocortisone and cortisone acetate are based on pharmacokinetic studies (18, 40), suggested doses for synthetic steroids are based on estimates from older studies comparing the relative antiinflammatory properties of various glucocorticoids.

Monitoring of glucocorticoid replacement is mainly based on clinical grounds because a reliable biomarker for glucocorticoid activity has yet to be identified. Plasma ACTH cannot be used as a criterion for glucocorticoid dose adjustment. In primary adrenal insufficiency, ACTH is invariably high before the morning dose and rapidly declines with increasing cortisol levels after glucocorticoid ingestion (42, 43). Aiming at ACTH levels within the normal range, therefore, would invariably result in overreplacement. In secondary adrenal insufficiency, plasma ACTH is low and thus not informative. Urinary 24-h free cortisol excretion has been advocated for monitoring of replacement quality (44). However, after exogenous glucocorticoid administration, urinary cortisol excretion shows considerable interindividual variability. Also, after glucocorticoid absorption, cortisol-binding globulin is rapidly saturated, resulting in transient but pronounced increases in renal cortisol excretion. Thus, one cannot refer to normal ranges for healthy subjects when judging urinary cortisol excretion during replacement therapy for adrenal insufficiency. Some authors have suggested regular measurements of serum cortisol day curves to monitor replacement therapy (44, 45). However, the efficacy of this approach is not supported by controlled studies, and recent data indicate a poor correlation between clinical assessment and cortisol levels (46). Timed serum cortisol measurements can be of some value in selected patients, *e.g.* in case of suspected noncompliance or malabsorption; however, random serum cortisol measurements without information on the time of the hydrocortisone dose are not informative.

Thus, in the absence of objective parameters, the physician has to rely primarily on clinical judgment, carefully taking into account signs and symptoms potentially suggestive of glucocorticoid over- or underreplacement (Table 1), recognizing their relative lack of specificity. Glucocorticoid underreplacement bears the risk of incipient crisis and significant impairment of well-being. Conversely, chronic overreplacement may lead to substantial morbidity, including impaired glucose tolerance, obesity, and osteoporosis. An increased incidence of osteoporosis has only been reported in patients receiving daily replacement doses of 30 mg hydrocortisone or higher (41, 47, 48) or 7.5 mg prednisone (41), whereas appropriate replacement doses of 20–25 mg hydrocortisone do not affect bone mineral density (46, 49). Therefore, bone mineral density measurements are not routinely required in patients with adrenal insufficiency receiving recommended glucocorticoid replacement doses.

Mineralocorticoid replacement

Patients with primary adrenal insufficiency require mineralocorticoid replacement, which usually consists of the oral administration of 9 α -fludrocortisone; fluorination at the 9 α position ensures selective binding to the mineralocorticoid receptor and thus exclusive mineralocorticoid action. By contrast, cortisol binds with equal affinity to both the glucocorticoid and the mineralocorticoid receptor. However, excessive MR binding of cortisol in the kidney is prevented by 11 β -hydroxysteroid dehydrogenase type 2, which inactivates cortisol to cortisone. Oelkers *et al.* (50) coined the term “mineralocorticoid unit (MCU),” determining that 100 MCU are equivalent to 100 μ g fludrocortisone and 40 mg hydrocortisone, respectively. By contrast, prednisolone exerts only reduced and dexamethasone exerts no mineralocorticoid activity at all; therefore, patients treated with synthetic glucocorticoids need particularly careful monitoring of their mineralocorticoid replacement.

In the newly diagnosed patient mineralocorticoid replacement should be initiated at 100 μ g once daily (Table 1); optimized doses may vary between 50 and 250 μ g. Children, in particular neonates and infants, have considerably higher mineralocorticoid dose requirements and often need additional salt supplementation. However, among adults there is also a good degree of interindividual variability. A high dietary salt intake may slightly reduce mineralocorticoid requirements. An important additional factor is temperature and humidity, *e.g.* individuals living in Mediterranean summer or tropical climates will require a 50% increase in fludrocortisone dose due to increased salt loss through perspiration. Monitoring (Table 1) includes supine and erect blood pressure and serum sodium and potassium; plasma renin activity should be checked regularly, aiming at the upper normal range (50). If essential hypertension develops, mineralocorticoid dose may be slightly reduced, accompanied by monitoring of serum sodium and potassium, but complete cessation of mineralocorticoid replacement should be avoided. It is important to recognize that plasma renin physiologically increases during pregnancy; therefore, monitoring in pregnancy should comprise blood pressure, serum sodium and potassium and, if required, urinary sodium excretion. During the last term of pregnancy fludrocortisone dose may require adjustment, also due to increased progesterone levels exerting anti-mineralocorticoid activity (51).

Prevention of Adrenal Crisis

Risk of adrenal crisis is higher in primary adrenal insufficiency, and several factors such as coincident APS or age have been suggested as additional modifiers (1, 52). Many crises are due to glucocorticoid dose reduction or lack of stress-related glucocorticoid dose adjustment by patients or general practitioners (1). All patients and their partners should receive regular crisis prevention training including verification of steroid emergency card/bracelet and instruction on stress-related glucocorticoid dose adjustment (Table 1). Generally, hydrocortisone should be doubled during intercurrent illness, such as a respiratory infection with fever, until clinical recovery. Gastrointestinal infec-

tions, a frequent cause of crisis, may require parenteral hydrocortisone administration. Preferably all patients, but at least patients traveling or living in areas with limited access to acute medical care, should receive a hydrocortisone emergency self-injection kit (*e.g.* 100 mg Solu-Cortef for im injection). For major surgery, trauma, delivery, and diseases requiring intensive care unit monitoring, patients should receive iv administration of 100–150 mg hydrocortisone per 24 h in 5% glucose or 25–50 mg hydrocortisone im four times daily. Some authors have advocated lower doses (25–75 mg/24 h) for surgical stress (53). However, 60 yr after the seminal observation that glucocorticoid replacement needs to be increased during periods of major stress (54), studies clarifying exact dose requirements are still outstanding.

DHEA replacement

The introduction of DHEA, the third major steroid produced by the adrenal gland, into the replacement regimen for adrenal insufficiency (55) represents a major advance, in particular for women who are invariably androgen deficient (55, 56). DHEA has been shown to significantly enhance well-being, mood, and subjective health status in women with primary and secondary adrenal insufficiency (55, 57–60) and also recently in children and adolescents with adrenal failure (61). Similar effects have been described for testosterone replacement in hypopituitarism (62); however, no study has yet directly compared DHEA to testosterone. In addition to acting as an androgen precursor, DHEA has neurosteroidal properties, exerting a primarily antidepressive effect, and also shows immunomodulatory properties (63). Of note, DHEA has been shown to exert beneficial effects on subjective health status and energy levels not only in women but also in men with primary adrenal insufficiency (58, 59), including significant beneficial effects on bone mineral density and truncal lean mass (58).

Currently, DHEA replacement is hampered by the lack of pharmaceutically controlled preparations, with questionable quality and content of several over-the-counter preparations (64). At present, DHEA should be reserved for patients with adrenal insufficiency suffering from significant impairment in well-being despite otherwise optimized replacement, in particular women with signs of androgen deficiency such as dry and itchy skin and loss of libido. DHEA should be taken as a single dose (25–50 mg) in the morning. Treatment monitoring (Table 1) should include blood sampling 24 h after the last preceding morning dose for measurement of serum DHEAS (in women, also androstenedione, testosterone, and SHBG) aiming at the middle normal range for healthy young subjects. I usually start patients on 25 mg and increase to 50 mg after 2 to 4 wk, advising them to halve the dose if androgenic skin side effects (greasy skin, spots) persist for more than 1 wk. Obviously, transdermal testosterone represents an alternative androgen replacement tool in women with adrenal failure.

Quality of Life, Disablement, and Prognosis

Recent data demonstrate that current standard replacement fails to restore quality of life, which is significantly impaired in pa-

tients with both primary and secondary adrenal insufficiency (34, 65, 66), with no apparent difference between prednisolone- and hydrocortisone-treated patients (67). Predominant complaints are fatigue, lack of energy, depression, anxiety, and reduced ability to cope with daily demands; the degree of impairment is comparable to that observed in congestive heart failure and chronic hemodialysis patients (34, 65). Subjective health status is most reduced in younger patients, but all age groups are significantly impaired (65), a persistent finding even if only analyzing patients without any comorbidity (65). This also has a socioeconomic perspective because patients with Addison's disease have a 2- to 3-fold higher likelihood of receiving disablement pensions (34, 65).

In addition, recent large cohort studies have demonstrated an increased mortality not only in patients with secondary adrenal insufficiency due to hypopituitarism (68) but also in primary adrenal insufficiency, *i.e.* Addison's disease (69, 70), a finding still valid when the influence of comorbidities is excluded. The causes underlying this increased mortality remain unclear, but we certainly need to consider the possible impact of current replacement regimens on the observed increase in mortality from cardiovascular and cerebrovascular disease and respiratory infections.

Returning to the Patient

The patient is a young man with acute primary adrenal insufficiency of autoimmune origin; his presentation with adrenal crisis is likely to have been precipitated by coexisting overt hyperthyroidism. He improved quickly after saline infusion and initiation of hydrocortisone treatment at major stress doses that took into account the increase in cortisol clearance due to hyperthyroidism. His thyroid function normalized shortly after initiation of carbimazole treatment, which was continued for 12 months. He was discharged after 1 wk on 30 mg hydrocortisone and 100 μ g fludrocortisone; hydrocortisone was reduced to 25 mg at his first outpatient review 4 wk after discharge. Two years after diagnosis, he is doing well on chronic replacement with 20 mg hydrocortisone and 150 μ g fludrocortisone, he has a body mass index of 21 kg/m², and he attends college. He has not suffered an adrenal crisis since his initial presentation, and his thyroid function remains normal.

Conclusions

More than 150 yr after Thomas Addison (71) first described a disease characterized by salt wasting and hyperpigmentation as the result of adrenal gland destruction, adrenal insufficiency is no longer an invariably fatal condition. The landmark achievement of the synthesis of cortisone in the late 1940s and its introduction into therapy in the early 1950s quickly lead to widespread availability of life-saving glucocorticoid replacement therapy. However, whereas initial survival is routinely achieved nowadays, current replacement regimens may not be able to achieve normal quality of life. Future research has to uncover the causes under-

lying the increased mortality in adrenal insufficiency and should further explore the role of novel replacement modalities, such as DHEA and modified-release hydrocortisone.

Acknowledgments

Address all correspondence and requests for reprints to: Wiebke Arlt, M.D., D.Sc., FRCP, Professor of Medicine, Medical Research Council Senior Clinical Fellow, School of Clinical and Experimental Medicine, University of Birmingham, Institute of Biomedical Research, Room 225, Wolfson Drive, Birmingham B15 2TT, United Kingdom. E-mail: w.arlt@bham.ac.uk.

W.A. is supported by the Medical Research Council UK (Senior Clinical Fellowship G116/172).

Disclosure Summary: The author has nothing to disclose.

References

1. Arlt W, Allolio B 2003 Adrenal insufficiency. *Lancet* 361:1881–1893
2. Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C 2005 Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab* 90:3243–3250
3. Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM 2006 The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab* 91:43–47
4. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL 1988 A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet* 1:1208–1210
5. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM 1998 Defining the normal cortisol response to the short synacthen test: implications for the investigation of hypothalamic-pituitary disorders. *Clin Endocrinol (Oxf)* 49: 287–292
6. Inder WJ, Hunt PJ 2002 Glucocorticoid replacement in pituitary surgery: guidelines for perioperative assessment and management. *J Clin Endocrinol Metab* 87:2745–2750
7. Arlt W, Justl HG, Callies F, Reincke M, Hubler D, Oettel M, Ernst M, Schulte HM, Allolio B 1998 Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression. *J Clin Endocrinol Metab* 83:1928–1934
8. Betterle C, Dal Pra C, Mantero F, Zanchetta R 2002 Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev* 23:327–364
9. Ahonen P, Myllärniemi S, Sipilä I, Perheentupa J 1990 Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med* 322:1829–1836
10. Finnish-German APECED Consortium 1997 An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet* 17:399–403
11. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Laloti MD, Mullis PE, Antonarakis SE, Kawasaki K, Asakawa S, Ito F, Shimizu N 1997 Positional cloning of the APECED gene. *Nat Genet* 17:393–398
12. Mathis D, Benoist C 2007 A decade of AIRE. *Nat Rev Immunol* 7:645–650
13. Kemp EH, Ajjan RA, Husebye ES, Peterson P, Uibo R, Imrie H, Pearce SH, Watson PF, Weetman AP 1998 A cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphism is associated with autoimmune Addison's disease in English patients. *Clin Endocrinol (Oxf)* 49:609–613
14. Skinningsrud B, Husebye ES, Gervin K, Løvås K, Blomhoff A, Wolff AB, Kemp EH, Egeland T, Undlien DE 2008 Mutation screening of PTPN22: association of the 1858T-allele with Addison's disease. *Eur J Hum Genet* 16:977–982
15. Skinningsrud B, Husebye ES, Pearce SH, McDonald DO, Brandal K, Wolff AB, Løvås K, Egeland T, Undlien DE 2008 Polymorphisms in CLEC16A and CIITA at 16p13 are associated with primary adrenal insufficiency. *J Clin Endocrinol Metab* 93:3310–3317
16. Hangaard J, Andersen M, Grodum E, Koldkjaer O, Hagen C 1996 Pulsatile

- thyrotropin secretion in patients with Addison's disease during variable glucocorticoid therapy. *J Clin Endocrinol Metab* 81:2502–2507
17. Topless DJ, White EL, Stockigt JR 1980 Significance of thyrotropin excess in untreated primary adrenal insufficiency. *J Clin Endocrinol Metab* 50:52–56
 18. Allolio B, Kaulen D, Deuss U, Hipp FX, Winkelmann W 1985 Comparison between hydrocortisone and cortisone acetate as replacement therapy in adrenocortical insufficiency. *Akt Endokr Stoffw* 6:35–39
 19. Lutz A, Stojkovic M, Schmidt M, Arlt W, Allolio B, Reincke M 2000 Adrenocortical function in patients with macrometastases of the adrenal gland. *Eur J Endocrinol* 143:91–97
 20. Lam KY, Lo CY 2002 Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. *Clin Endocrinol (Oxf)* 56:95–101
 21. Presotto F, Fornasini F, Betterle C, Federspil G, Rossato M 2005 Acute adrenal failure as the heralding symptom of primary antiphospholipid syndrome: report of a case and review of the literature. *Eur J Endocrinol* 153:507–514
 22. Moser HW, Mahmood A, Raymond GV 2007 X-linked adrenoleukodystrophy. *Nat Clin Pract Neurol* 3:140–151
 23. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, Thompson CJ 2004 Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab* 89:4929–4936
 24. Giordano G, Aimaretti G, Ghigo E 2005 Variations of pituitary function over time after brain injuries: the lesson from a prospective study. *Pituitary* 8:227–231
 25. Chanson P, Lepeintre JF, Ducreux D 2004 Management of pituitary apoplexy. *Expert Opin Pharmacother* 5:1287–1298
 26. Schwedt TJ, Matharu MS, Dodick DW 2006 Thunderclap headache. *Lancet Neurol* 5:621–631
 27. Caturegli P, Lupi I, Landek-Salgado M, Kimura H, Rose NR 2008 Pituitary autoimmunity: 30 years later. *Autoimmun Rev* 7:631–637
 28. Kasperlik-Zaluska AA, Czarnocka B, Czech W 2003 Autoimmunity as the most frequent cause of idiopathic secondary adrenal insufficiency: report of 111 cases. *Autoimmunity* 36:155–159
 29. Manetti L, Lupi I, Morselli LL, Albertini S, Cosottini M, Grasso L, Genovesi M, Pinna G, Mariotti S, Bogazzi F, Bartalena L, Martino E 2007 Prevalence and functional significance of antipituitary antibodies in patients with autoimmune and non-autoimmune thyroid diseases. *J Clin Endocrinol Metab* 92:2176–2181
 30. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL 1991 Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab* 72:39–45
 31. Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, Tucker GT, Ross RJ 2004 Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. *Clin Endocrinol (Oxf)* 61:367–375
 32. Krieger DT, Allen W, Rizzo F, Krieger HP 1971 Characterization of the normal temporal pattern of plasma corticosteroid levels. *J Clin Endocrinol Metab* 32:266–284
 33. Plat L, Leproult R, L'Hermite-Baleriaux M, Fery F, Mockel J, Polonsky KS, Van Cauter E 1999 Metabolic effects of short-term elevations of plasma cortisol are more pronounced in the evening than in the morning. *J Clin Endocrinol Metab* 84:3082–3092
 34. Lovas K, Loge JH, Husebye ES 2002 Subjective health status in Norwegian patients with Addison's disease. *Clin Endocrinol (Oxf)* 56:581–588
 35. Lovas K, Husebye ES, Holsten F, Bjorvatn B 2003 Sleep disturbances in patients with Addison's disease. *Eur J Endocrinol* 148:449–456
 36. Merza Z, Rostami-Hodjegan A, Memmott A, Doane A, Ibbotson V, Newell-Price J, Tucker GT, Ross RJ 2006 Circadian hydrocortisone infusions in patients with adrenal insufficiency and congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)* 65:45–50
 37. Lovas K, Husebye ES 2007 Continuous subcutaneous hydrocortisone infusion in Addison's disease. *Eur J Endocrinol* 157:109–112
 38. Newell-Price J, Whiteman M, Rostami-Hodjegan A, Darzy K, Shalet S, Tucker GT, Ross RJ 2008 Modified-release hydrocortisone for circadian therapy: a proof-of-principle study in dexamethasone-suppressed normal volunteers. *Clin Endocrinol (Oxf)* 68:130–135
 39. Debono M, Ghobadi C, Rostami-Hodjegan A, Huatan H, Campbell MJ, Newell-Price J, Darzy K, Merke DP, Arlt W, Ross RJ 2009 Modified-release hydrocortisone to provide circadian cortisol profiles. *J Clin Endocrinol Metab*. 2009 Feb 17 [Epub ahead of print]
 40. Kehlet H, Binder C, Blichert-Toft M 1976 Glucocorticoid maintenance therapy following adrenalectomy: assessment of dosage and preparation. *Clin Endocrinol (Oxf)* 5:37–41
 41. Jodar E, Valdepenas MP, Martinez G, Jara A, Hawkins F 2003 Long-term follow-up of bone mineral density in Addison's disease. *Clin Endocrinol (Oxf)* 58:617–620
 42. Feek CM, Ratcliffe JG, Seth J, Gray CE, Toft AD, Irvine WJ 1981 Patterns of plasma cortisol and ACTH concentrations in patients with Addison's disease treated with conventional corticosteroid replacement. *Clin Endocrinol (Oxf)* 14:451–458
 43. Scott RS, Donald RA, Espiner EA 1978 Plasma ACTH and cortisol profiles in Addisonian patients receiving conventional substitution therapy. *Clin Endocrinol (Oxf)* 9:571–576
 44. Howlett TA 1997 An assessment of optimal hydrocortisone replacement therapy. *Clin Endocrinol (Oxf)* 46:263–268
 45. Peacey SR, Guo CY, Robinson AM, Price A, Giles MA, Eastell R, Weetman AP 1997 Glucocorticoid replacement therapy: are patients over treated and does it matter? *Clin Endocrinol (Oxf)* 46:255–261
 46. Arlt W, Rosenthal C, Hahner S, Allolio B 2006 Quality of glucocorticoid replacement in adrenal insufficiency: clinical assessment vs. timed serum cortisol measurements. *Clin Endocrinol (Oxf)* 64:384–389
 47. Zelissen PM, Croughs RJ, van Rijk PP, Raymakers JA 1994 Effect of glucocorticoid replacement therapy on bone mineral density in patients with Addison disease. *Ann Intern Med* 120:207–210
 48. Florkowski CM, Holmes SJ, Elliot JR, Donald RA, Espiner EA 1994 Bone mineral density is reduced in female but not male subjects with Addison's disease. *N Z Med J* 107:52–53
 49. Braatvedt GD, Joyce M, Evans M, Clearwater J, Reid IR 1999 Bone mineral density in patients with treated Addison's disease. *Osteoporos Int* 10:435–440
 50. Oelkers W, Diederich S, Bahr V 1992 Diagnosis and therapy surveillance in Addison's disease: rapid adrenocorticotropin (ACTH) test and measurement of plasma ACTH, renin activity, and aldosterone. *J Clin Endocrinol Metab* 75:259–264
 51. Ehrlich EN, Lindheimer MD 1972 Effect of administered mineralocorticoids or ACTH in pregnant women. Attenuation of kaliuretic influence of mineralocorticoids during pregnancy. *J Clin Invest* 51:1301–1309
 52. Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, Berg JP, Mella B, Husebye ES 2009 Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. *Eur J Endocrinol* 160:233–237
 53. Glowinski JV, Loriaux DL 1997 A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. *Surgery* 121:123–129
 54. Nicholas JA, Burstein CL, Umberger CJ, Wilson PD 1955 Management of adrenocortical insufficiency during surgery. *AMA Arch Surg* 71:737–742
 55. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, Huebler D, Oettel M, Ernst M, Schulte HM, Allolio B 1999 Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 341:1013–1020
 56. Miller KK, Sesmilo G, Schiller A, Schoenfeld D, Burton S, Klibanski A 2001 Androgen deficiency in women with hypopituitarism. *J Clin Endocrinol Metab* 86:561–567
 57. Brooke AM, Kalingag LA, Miraki-Moud F, Camacho-Hübner C, Maher KT, Walker DM, Hinson JP, Monson JP 2006 Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 91:3773–3779
 58. Gurnell EM, Hunt PJ, Curran SE, Conway CL, Pullenayegum EM, Huppert FA, Compston JE, Herbert J, Chatterjee VK 2008 Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab* 93:400–409
 59. Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, Herbert J, Chatterjee VK 2000 Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 85:4650–4656
 60. Johannsson G, Burman P, Wirén L, Engström BE, Nilsson AG, Ottosson M, Jonsson B, Bengtsson BA, Karlsson FA 2002 Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. *J Clin Endocrinol Metab* 87:2046–2052
 61. Binder G, Weber S, Ehrismann M, Zaier N, Meisner C, Ranke MB, Maier L, Wudy SA, Hartmann MF, Heinrich U, Bettendorf M, Doerr HG, Pfäffle RW, Keller E; the South German Working Group for Pediatric Endocrinology 2009 Effects of dehydroepiandrosterone therapy on pubic hair growth and psychological well-being in adolescent girls and young women with central adrenal insufficiency: a double-blind, randomized, placebo-controlled phase III trial. *J Clin Endocrinol Metab* 94:1182–1190
 62. Miller KK, Biller BM, Beauregard C, Lipman JG, Jones J, Schoenfeld D, Sherman JC, Swearingen B, Loeffler J, Klibanski A 2006 Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 91:1683–1690

63. Arlt W 2006 Androgen therapy in women. *Eur J Endocrinol* 154:1–11
64. Parasrampur J, Schwartz K, Petesch R 1998 Quality control of dehydroepiandrosterone dietary supplement products. *JAMA* 280:1565
65. Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, Decker O, Arlt W, Allolio B 2007 Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. *J Clin Endocrinol Metab* 92:3912–3922
66. Thomsen AF, Kvist TK, Andersen PK, Kessing LV 2006 The risk of affective disorders in patients with adrenocortical insufficiency. *Psychoneuroendocrinology* 31:614–622
67. Bleicken B, Hahner S, Loeffler M, Ventz M, Allolio B, Quinkler M 2008 Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens. *Eur J Endocrinol* 159:811–817
68. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart PM 2001 Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 357:425–431
69. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G 2006 Premature mortality in patients with Addison's disease: a population-based study. *J Clin Endocrinol Metab* 91:4849–4853
70. Bensing S, Brandt L, Tabaroj F, Sjöberg O, Nilsson B, Ekbom A, Blomqvist P, Kämpe O 2008 Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. *Clin Endocrinol (Oxf)* 69:697–704
71. Addison T 1855 On the constitutional and local effects of diseases of the supra-renal capsules. London: Warren and Son