

## The Approach to the Adult with Newly Diagnosed Adrenal Insufficiency

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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/m<sup>2</sup>), 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 T<sub>4</sub>, 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.

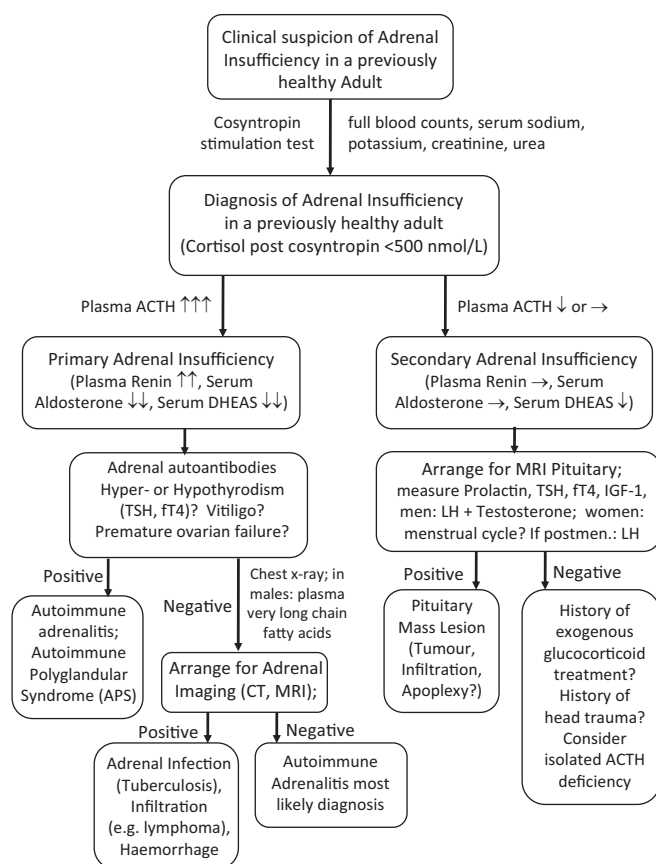
In our patient, primary adrenal insufficiency is confirmed by very high ACTH levels, also reflected by hyperpigmentation in areas of increased shear stress to the skin. In addition, his thyroid function test results revealed overt hyperthyroidism, thus making a *prima facie* case for autoimmune polyglandular 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<br>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<br>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<br>Secondary adrenal insufficiency: 15–20 mg hydrocortisone per 24 h; if borderline fail in cosyntropin test consider 10 mg or stress dose cover only<br>Administer in two to three divided doses with two thirds and half of the dose, respectively, administered immediately after waking up<br>Monitoring:<br><ul style="list-style-type: none"> <li>• Check body weight, calculate body mass index</li> <li>• Check for signs of underreplacement (weight loss, fatigue, nausea, myalgia, lack of energy)</li> <li>• Check for signs of overreplacement (weight gain, central obesity, stretch marks, osteopenia/osteoporosis, impaired glucose tolerance, hypertension)</li> <li>• Take a detailed account of stress-related glucocorticoid dose self-adjustments since last visit, potential adverse events including emergency treatment and/or hospitalization</li> </ul>                              |
| Mineralocorticoid replacement      | Only required in primary adrenal insufficiency<br>Not required as long as hydrocortisone dose >50 mg per 24 h<br>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<br>Monitoring:<br><ul style="list-style-type: none"> <li>• Blood pressure sitting and erect (postural drop ≥20 mm Hg indicative of underreplacement, high blood pressure may indicate overreplacement)</li> <li>• Check for peripheral edema (indicative of overreplacement)</li> <li>• Check serum sodium and potassium</li> <li>• 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)</li> </ul>   |
| 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)<br>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)<br>Monitoring:<br><ul style="list-style-type: none"> <li>• In women, serum testosterone and SHBG (to calculate free androgen index)</li> <li>• In men and women on DHEA replacement, serum DHEAS and androstenedione levels</li> <li>• Blood should be sampled at steady state, i.e. 12–24 h after the last preceding DHEA dose</li> </ul>  |
| Additional monitoring requirements | Regular follow-up in specialist center every 6 to 12 months<br>In primary adrenal insufficiency of autoimmune origin (isolated Addison or APS)<br>Serum TSH every 12 months<br>In female patients: check regularity of menstrual cycle, consider measurement of ovarian autoantibodies if family planning not finalized<br>Check emergency bracelet/steroid card, update as required<br>Check knowledge of “sick day rules” and reinforce emergency guidelines involving partner/family members<br>Consider prescription of a hydrocortisone emergency self-injection kit, in particular if delayed access to acute medical care is likely (rural areas, travel)<br>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 T<sub>4</sub> replacement therapy in the setting of acute adrenal insufficiency because an increase in T<sub>4</sub> 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 T<sub>4</sub>.

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/m<sup>2</sup> (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 $\beta$ -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 T<sub>4</sub> 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 $\beta$ -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 $\alpha$ -fludrocortisone; fluorination at the 9 $\alpha$  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 $\beta$ -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  $\mu$ 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  $\mu$ g once daily (Table 1); optimized doses may vary between 50 and 250  $\mu$ 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  $\mu$ 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  $\mu$ g fludrocortisone, he has a body mass index of 21 kg/m<sup>2</sup>, 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.

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