

# Cortisol Deficiency: Frequent, Life-Impairing, and How to Give Patients Their Lives Back by Correcting It, Part 2

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Part 1 that discusses the signs and symptoms of cortisol deficiency appears in the January 2018 issue and is also available online.

## To Treat or Not to Treat Cortisol Deficiency?

People with cortisol deficiency who do not get treatment continue suffering from the psychic and physical consequences of cortisol deficiency at every moment of their lives. In the long term, the absence of treatment permits the cortisol deficiency to aggravate and produce chronic inflammatory diseases such as rheumatoid arthritis and psychological disorders, from irritability to the extreme form of paranoid psychosis. Because of the adverse consequences of not treating cortisol deficiency, forgoing treatment is not really an option.

## Natural Treatments to Improve Cortisol Levels

The first natural treatment to get a higher cortisol level is to increase light.<sup>154</sup> After moving from a dark room into full daylight, an individual's cortisol level increases by 50% or more within minutes. Thus, the golden rule is to expose oneself to more light: switching all the lights on in the office and at home and going outdoors at least once a day in full daylight for a minimum of half an hour. This quickly increases not only cortisol levels but also the number of cortisol receptors.

Second, it is of great importance to breathe cleaner air and eat organic foods to avoid airborne and foodborne pollutants, as toxins usually aggress the zona fasciculata of the adrenal glands that produces cortisol or block the target cells' glucocorticoid receptors, inhibiting part of the action of cortisol.

One of these irritant pollutants is formaldehyde,<sup>155</sup> which pollutes many homes and offices. It is part of many types of glue that fix floor coverings to the ground and bind compressed wood together in home and office furniture. It is often part of plastic carpets and toys and slowly outgasses from these objects into the indoor atmosphere over the years, being inhaled through breathing. What to do about it? Apart from getting rid of these formaldehyde-containing materials inside homes, simply open the windows in rooms where such materials are and let outdoor air enter. Regularly ventilating rooms with outdoor air drastically reduces the formaldehyde concentration in the indoor air and, thus, the risk of adrenal gland damage.

Third, increasing the consumption of protein-rich foods,<sup>156-157</sup> such as meat, poultry, and fish, and fat-rich foods,<sup>158-161</sup> such as eggs, yolk, butter (preferably clarified butter), liver, and other organ meats, elevates the cortisol production and level by providing the ingredients for production of cortisol. Augmenting protein is not always easy with patients with cortisol deficiency, as they tend to accumulate nitrogen in the blood by consuming these nitrogen-rich foods.

Indeed, once they consume meat and other protein-rich foods, the high level of nitrogen in their blood (azotemia) gives them nausea and disgust for meat. Fat intake also poses problems, as fats seem hard to digest by these patients, frequently causing indigestion. The solution consists of correcting the cortisol deficiency with a cortisol supplement and encouraging the patients to increase the intake of the protein- and fat-rich foods they tolerate.

People with cortisol deficiency should also avoid "bad" carbs, carbohydrate-rich foods that reduce the production of cortisol, like sweets, sugars,<sup>162</sup> unsprouted bread, muesli, porridge, and rice. These foods can reduce the secretion of cortisol by 20–40%, enough to create problems. If ever they give in to the temptation of a chocolate bar or soft drinks, let them do it after a healthy meal, which dilutes the sugar into a bigger volume, reducing sugar's hyperglycemic effect that blocks cortisol production (peak levels of glucose inhibit cortisol release).

Fourth, some rare nutritional supplements can help the adrenal glands function better, although modestly. Vitamin C is one of them.<sup>163-164</sup> With 500 mg to 2 g of vitamin C a day, the action of cortisol may get a boost. L-acetyl-carnitine, the activated form of L-carnitine, is another nutrient whose intake has been shown to significantly increase serum cortisol levels in humans.<sup>165</sup> A dose of 2 g/day may be efficient.

Fifth, several herbal extracts may weakly mimic cortisol activity by increasing its bioavailability and stimulating cortisol receptors, providing limited relief to adrenal-deficient patients. Plants also produce hormones that may have beneficial effects in humans. Extracts of licorice root may, for example, lessen complaints in patients with cortisol deficiency.<sup>166-167</sup> In my experience, licorice root extract has about 10-25% of the beneficial action of an adequate cortisol or hydrocortisone treatment.

Sixth, as the storage of cortisol in the adrenal glands is small in patients with adrenal deficiency, these patients should avoid exposing themselves to any unnecessary stressors, which deplete the adrenals of their cortisol stores. Selecting jobs and leisure activities that do not put excessive strain on the adrenal glands may be a wise decision for people who do not get or want to take a cortisol treatment. Spiritual meditation has been reported to be helpful in improving cortisol levels. Regular meditators respond to stressful conditions with a greater production of cortisol than non-meditators, while the cortisol level is lower in resting states, minimizing spillage.<sup>168</sup>

Table 1 summarizes the main interventions you can do yourself with the help of a nutritionist to improve your cortisol secretion.

**Table 1. Interventions to Improve Cortisol Secretion**

- Increase light: daylight, intense indoor light, sunny holiday resorts
- Increase fat-rich foods (butter, egg yolk, liver, etc.)
- Take vitamin C supplements: 0.5 to 2 g/day
- Avoid indoor pollutants: stay away from plastic furniture or floor coverings, wood preservatives; keep windows open
- Reduce unhealthy carbohydrate-rich foods (sugar, sweets, chocolate, unsprouted bread, muesli, porridge, rice, pasta, soft drinks, alcohol)
- Herbal extract of licorice root: 450 to 1800 mg/day
- Increase protein-rich foods (fish, poultry, meat)
- Increase fruit intake (contains vitamin C, which may increase adrenal function)
- Avoid unnecessary stressful conditions (which deplete cortisol stores); regularly relax or meditate

## Glucocorticoid Treatment of Cortisol Deficiency

Glucocorticoid is the common name given to the whole family of natural or synthetically produced cortisol-like molecules, which share the property of increasing the blood sugar levels. "Gluco" means "glucose" (sugar), and "corticoid" signifies that it "comes from the cortex," the outer part of the adrenal glands that produces this type of hormone. The human body makes two major bioidentical glucocorticoids: cortisol and cortisone. Bioidentical means that these hormones have the same molecular structure as the body's own corresponding compounds. Corticosterone, which in rodents is more potent than cortisol, is another natural hormone that is found in humans.

Cortisol, also called hydrocortisone when it is used in therapy, is the body's most potent glucocorticoid hormone. Cortisone is the precursor glucocorticoid made by the adrenals. It has 80% of cortisol's action. Supplementation with cortisone is therefore always at a slightly higher dosage than with cortisol or hydrocortisone to get the same effects: To do the same job, 25 mg per day of cortisone is needed where the body requires 20 mg of hydrocortisone.

However, the name cortisone is misleadingly used nowadays to name synthetic derivatives of cortisol, such as prednisone and methylprednisolone. These compounds are not identical to the body's own cortisol and cortisone. They may have different effects and indications. They are also used at lower dosages, as they have more potent effects.

Bioidentical glucocorticoids have better psychological effects and improve the blood pressure better than synthetic derivatives. The use of bioidentical cortisol and cortisone is indicated to treat most cases of cortisol deficiency,

particularly when the predominant complaints are psychological. Bioidentical glucocorticoids better improve the mind, mood, energy, stress resistance, and other personality features compared to non-bioidentical glucocorticoids<sup>169-172</sup> because they are entirely adapted to the human body, particularly its glucocorticoid receptors.

Hydrocortisone is also a better choice to treat arterial hypotension because it retains salt and water more than synthetic derivatives.

## Safety of Bioidentical Hormones

Because cortisol and cortisone are completely adapted to the human body, they are also safer. The risk of side effects such as skin atrophy is lower with these bioidentical glucocorticoids than with synthetic derivatives.<sup>173</sup> Long-term behavioral outcome and neuromotor development are also better in children who neonatally have received hydrocortisone rather than synthetic dexamethasone to avoid bronchial dysplasia.<sup>172</sup> Whenever side effects, usually overdose symptoms, occur with these natural compounds, they persist for a shorter time (6-24 hours) because of a quicker breakdown and inactivation by the body than when caused by synthetic derivatives (a few days). For this reason, at comparable doses, cortisol and cortisone reduce the endogenous cortisol production of the adrenal glands considerably less than synthetic derivatives. The risk of adrenal gland suppression is also less with bioidentical glucocorticoids.<sup>51,174-175</sup>

Table 2 (adapted from Chrousos et al., 2011)<sup>51</sup> shows that synthetic derivatives of cortisol at equivalent doses suppress the adrenal glands more. The greater their glucocorticoid (and thus anti-inflammatory) potency, the more they suppress the endogenous cortisol secretion.

**Table 2. Comparison of Synthetic Cortisol Derivatives**

Glucocorticoids	Equivalent dose	Glucocorticoid potency	Hypothalamo-pituitary-adrenal axis suppression	Biologic half-life
Cortisol	20 mg	1.0	1x	8-12 h
Prednisone	5 mg	4.0	4x	18-36 h
Triamcinolone	4 mg	5.0	4x	18-36 h
Methylprednisolone	4 mg	5.0	4x	18-36 h
Dexamethasone	0.375 mg	30	8.5x	36-54 h

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➤ The safety of all these glucocorticoids is greatly increased with the use of lower doses of glucocorticoids, such as 30 mg/day or less of hydrocortisone and 5 mg/day or less of prednisolone.<sup>28</sup>

Non-bioidentical glucocorticoids reduce inflammation better but may suppress the adrenal glands more. Non-bioidentical glucocorticoids, such as prednisone, prednisolone, methylprednisolone, and dexamethasone, are more indicated than bioidentical cortisol whenever inflammation prevails. Indeed, these compounds reduce inflammation more efficiently and persistently due to their (much) longer duration of action, usually 24 hours or more after intake (see table above).<sup>51,56,176-178</sup> A good strategy is to prescribe them for a limited time (2–6 months is the time necessary to reduce the inflammation) and then switch to bioidentical cortisol once the inflammation is gone.

As previously mentioned, there are two bioidentical hormones available at pharmacies: cortisol (usually delivered under its synonym, hydrocortisone) and cortisone (the precursor to cortisol, with 20% less potency). In most cases, for patients with no tendency toward high blood pressure, being overweight, or swelling of the feet, hydrocortisone is the preferred treatment.<sup>179</sup> The science behind bioidentical cortisol treatment is strong. Pubmed, the main Internet medical databank, presents 270 placebo-controlled studies in adults (almost all double-blind; 256 with systemic therapies,<sup>180-433</sup> 14 with topical therapies<sup>434-447</sup>).

### Daily Cortisol Production

How much cortisol do humans produce? Researchers have found that the cortisol production rate in sedentary adults assessed in an in-hospital resting

unit is on average more in men (22.5 mg per 24 hours) than in women (9.2 mg per 24 hours)<sup>448</sup> due to the bigger body surface area and adrenal glands of men. The average body surface area is 1.9 m<sup>2</sup> in men and 1.6 m<sup>2</sup> in women.<sup>449</sup> Other investigators have found lower cortisol levels in men, an average of 9.1-10.9 mg/m<sup>2</sup> of the body,<sup>450-451</sup> which equals about 17.3- 20.7 mg/day of cortisol for men with average body surface area.

However, these productions are valid only for sedentary resting conditions in laboratory units. In real life, the multiple mental and physical activities and higher stress conditions require and stimulate the adrenal glands to produce more cortisol. An average day in “real life” conditions requires at least 30–50% more cortisol production so that the real daily average cortisol production is probably 30 mg/day in men and 20 mg/day in women.

In people with heavy physical activity, daily cortisol production may even triple. Urinary cortisol excretion in female long-distance runners, for example, is threefold higher than that in sedentary persons.<sup>452</sup>

How much cortisol do cortisol-deficient patients need? My personal experience is that doses of less than 15 mg/day in female and less than 20 mg/day in male cortisol-deficient adults, respectively, do not work well. At too-low doses, patients feel – after an initial modest and short improvement in cortisol activity two-to-four hours after intake – a noticeable drop in energy, due to a fall in cortisol activity. Low doses of 5–10 mg/day of cortisol are just not sufficient to keep the baseline cortisol levels high enough for a satisfying quality of life.

How much cortisol is absorbed after intestinal intake? Does this mean that we need a maximum of 20 to 30 mg per day cortisol intake to correct a near total deficiency? No, because, on average, less than half – only 43% – of oral

hydrocortisone (cortisol) is absorbed.<sup>453</sup> This means that a patient who does not have any cortisol production, needs to take a dose equivalent to double the normal endogenous cortisol production – 40 to 60 mg per day of oral hydrocortisone – to compensate for the absence of endogenous cortisol production.

In fact, cortisol absorption in the intestines might even be lower because the 43% of hydrocortisone absorption was measured in optimal conditions in which hydrocortisone was perfused with water in the intestinal lumen. The more water is added, the more hydrocortisone is absorbed. Thus, water intake may improve hydrocortisone absorption.

Food ingestion before hydrocortisone intake, on the other hand, delays hydrocortisone absorption.<sup>454</sup>

Divided doses of hydrocortisone usually, but not always, work better. For most patients, hydrocortisone should be taken in divided doses, at least twice a day,<sup>455-456</sup> for example, a higher dose in the morning after waking and the remaining dose during lunch. I recommend taking doses 5-20 minutes before breakfast and lunch, but some people experience stomach irritation because of the acetate that is bound to the hydrocortisone; it is pharmaceutically delivered as hydrocortisone acetate, which is an acid, and not as hydrocortisone alone. To avoid acidity, the hydrocortisone can be taken after meals or, if problems persist, prescribe the hydrocortisone pills with a protective (enteric coated) layer for the stomach.

Some people need to divide the doses further into three to four smaller portions taken at regular intervals throughout the day.<sup>454,456-458</sup> In these cases, they can take a supplementary dose of 5 mg of hydrocortisone at 4 p.m. and before bedtime. The 5 mg of hydrocortisone at bedtime is too small to keep the patient awake at night, but it does provide better energy upon waking the next morning.

What if a patient forgets the second dose of hydrocortisone or cortisone at lunch? He or she should take it later (4 p.m., for example), but not too late (after evening meal). Patients who tend to forget to take the second dose can try taking the full daily dose after

**Table 3. Glucocorticoid Hypertensive Potencies**

Glucocorticoids	Equivalent dose	Mineralocorticoid (water-retaining and hypertensive) potency
Cortisol	20 mg	1.0
Prednisone	5 mg	0.3
Methylprednisolone	4 mg	0

waking. Some people do fine and stay energized until bedtime; others do not and need two or even three bioidentical hydrocortisone or cortisone doses to feel well throughout the day.

### Treatment with Synthetic Glucocorticoid Derivatives

In inflammatory diseases, such as the flu and rheumatoid arthritis, the synthetic cortisol derivative prednisone and its active metabolite, prednisolone, provide more efficient relief and the ability to avoid permanent adverse consequences, such as joint deformations, thanks to their prolonged duration of action.<sup>51,459-460</sup>

In overweight people and individuals with a tendency to foot edema and arterial hypertension, permanent use of methylprednisolone is generally a better option because, at equivalent doses, it retains less water and weight and increases blood pressure less than other glucocorticoids, particularly much less than the bioidentical hydrocortisone. When I prescribe it, I start with a period of two to six months and may continue administering it if the patient remains prone to the aforementioned disorders.

Table 3 (adapted from Chrousos et al., 2011)<sup>51</sup> shows the absence at physiological dose of the water-retaining and blood pressure-increasing effect of methylprednisolone compared to cortisol and prednisone.

Dexamethasone is a potent synthetic derivative of cortisol. A dose of 0.25 mg of dexamethasone equals the activity of 20 mg of hydrocortisone. Because of its longer 48-hour duration of action, dexamethasone may considerably reduce adrenal hormone secretion, including the production of androgens (male hormones). Dexamethasone's

capacity to drastically reduce adrenal androgens is useful in reducing excessive body hair growth in women resulting from an excessive production of adrenal androgens. A once-daily morning intake of dexamethasone is usually sufficient to considerably suppress adrenal androgen production for more than 24 hours. I do not find its intake every two days efficient, as patients do not usually feel well on the second day, perhaps due to recurrence of adrenal deficiency.

To reduce skin rashes or to avoid keloid (voluminous scar) formation, a cream of 1-3% hydrocortisone may prove efficient. A concentration of 3% equals 30 mg of hydrocortisone per gram of cream. If this does not suffice, a lotion with a synthetic glucocorticoid derivative may help, but only if the area of skin application is small (several square centimeters), otherwise too much of the more potent synthetic derivative will penetrate through the skin into the body and cause side effects.

In emergencies, injections with high doses (50 to 250 mg) of cortisol or synthetic derivatives may be helpful, but this should be limited to exceptional cases as overdoses produce side effects. Table 4 summarizes the various cortisol treatments.

### Dealing with Inflammation, Infections, Allergies, or Stresses

In nature, vigorous adrenal glands react to stress by increasing their secretion of cortisol and other adrenal hormones. People with adrenal deficiency have lost a great part of their ability to produce additional amounts of cortisol in cases of extra need. Their inability to increase their secretion of cortisol explains why they suffer from stress much more than people with

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healthy adrenal glands. Their excessive stress sensitivity can progress into a real hate of any kind of stress.

The solution for these patients is to mimic nature by taking additional cortisol in conditions where more cortisol is needed. Taking a dose of 5 mg of hydrocortisone, 1.25 mg of prednisolone or prednisone, or 1 mg of methylprednisolone every 30 minutes until mild or moderately important infections or stressful feelings disappear may do the job.<sup>91,461</sup> In cases of severe inflammation or infection, this small dosage may have to be doubled. In most cases, stressful feelings and infections disappear within two hours. Continuously increasing every 30 minutes for more than three hours is not recommended. The total amount of cortisol that may be needed the day of an infection or heavy stress may be the double or triple of the regular daily dose without any side effects other than the disappearance of inflammation or stress.

Transiently increasing cortisol is really efficient when the increase is applied **in the minutes that the patient feels the first signs of infection or stress**. The longer patients wait to increase their doses, the less efficient this method becomes. When I start to get a sore throat, or feel my body aching because of the flu, even if it is in the middle of the night, I take an extra dose of hydrocortisone or, even better, switch to 1 to 2.5 mg prednisolone or prednisone every 30 minutes. These synthetic glucocorticoids are more efficient in alleviating flu symptoms thanks to their greater anti-inflammatory effects and prolonged 24-hour action. In general,

Table 4. Typical Glucocorticoid Treatment Schedules

Products	Average daily dose (usual dose range)		Morning	Typical schedule		
	Men	Women		Lunch	16h	Before bedtime
Hydrocortisone	30 mg (20-40 mg)	20 mg (15-30 mg)	10-20 mg	10 mg	(5 mg)	(5 mg)
Cortisone	37.5 mg (25-50 mg)	25 mg (20-37.5 mg)	12.5-25mg	12.5 mg	(6.25 mg)	(6.25 mg)
Prednisone, prednisolone	5 mg (2.5 -7.5 mg)	5 mg (2-6.75 mg)	5 mg	///////	///////	///////
Methylprednisolone	4 mg (2-6 mg)	4 mg (2-6 mg)	4 mg	///////	///////	///////
Dexamethasone	To ~ body hair growth in women; not for daily	0.35 mg (0.15-0.5 mg)	0.25 mg	///////	///////	///////

Note: In most cases, the dose between parentheses is not administered, but there are exceptions in which intake is necessary for patients to benefit from continuous cortisol.



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➤ one, two, or three additional intakes every 30 minutes are necessary to alleviate flu symptoms or a sore throat.

When patients wait too long after the start of an infection – two days for example – to increase their cortisol treatment, they often do better by limiting the increase in cortisol intake to an average of 50% more than their usual daily dose and must often continue this higher dose for three to ten days to rid themselves of the persisting infection, inflammation, or allergy. Such a prolonged intake of a higher dose of cortisol is generally unnecessary when the patient intervenes quickly and increases the dose in the minutes after noticing the first signs of an infection or allergy symptoms.

In stressful conditions, such as speaking at a meeting or participating in a radio or TV show, people with adrenal deficiency greatly benefit from taking 5–10 mg, 30 minutes to two hours before speaking. They experience more punch and perform better.

Can people not on glucocorticoid treatment occasionally take cortisol? Each time a person has a flu or another type of viral infection or has to face a stressful event, occasional intake of cortisol (preferable with an equal amount of protective DHEA) may stimulate the immune system without harm so that the infection is overcome in a matter of hours if the patient reacts quickly. A dose of 5-10 mg of hydrocortisone before a stressful event or 20-30 mg in one intake at the occasion of an infection may be sufficient to alleviate acute viral infections.

## Side Effects and Risks of Cortisol Treatment

Three types of side effects of cortisol treatment can occur:

- **Overdose effects** due to excessive cortisol levels.
- **Imbalance effects** due to an absence or deficiency in anabolic hormones, whose roles are to block any unwanted catabolic effects from cortisol.
- **Adrenal gland suppression** is when secretion of hormones by adrenal glands is partially or totally blocked by treatment through negative feedback to the pituitary gland's secretion of ACTH.

Total suppression of the hormone secretions of the adrenal glands usually occurs only with very high glucocorticoid doses that are considerably higher than those proposed in Table 4. Total adrenal suppression may endanger life in cases in which cortisol secretion stops suddenly, as life is not sustainable without cortisol.

In general, at 20 to 30 mg per day of hydrocortisone, adrenal suppression is only partial (20–35%) and transient. After stopping these physiological doses, patients recover their initial cortisol secretion within two to six weeks. However, when very high doses are given for four to six months, as with some patients with severe rheumatoid disorders, the decrease in adrenal secretion of cortisol may persist for eight months before returning to the initial state.

Neglecting to correct other hormone deficits and a high-carb diet may increase the need for higher cortisol doses. In my experience, patients whose rheumatism does not sufficiently respond to physiological doses of cortisol, in fact, have other hormone deficiencies (testosterone, estrogen, thyroid, DHEA, etc.) that contribute to their rheumatoid disorder. Their diets (sweets, artificial sweeteners, grains) trigger inflammation and block cortisol action. These

patients need to correct their diets and other hormone deficits, not to take pharmacological glucocorticoid doses.

## How to Stop a Treatment

Patients on long-term high glucocorticoid doses should never abruptly stop their treatments. Rather, they should slowly decrease the dose over a period of two to four months, lowering their dose by 5 mg/day of cortisol or 1-1.25 mg/day of synthetic glucocorticoid every 10-14 days. If this slow and gradual decrease in cortisol supplementation does not gradually revive adrenal glands, regular stimulation of adrenal production with intramuscular injections of 1–2 mg of long-acting ACTH twice a week may restore cortisol production in two to four months.

Table 5 presents an overview of the most frequent complaints and physical signs of glucocorticoid treatment excess.

## Additional Use of DHEA and Other Anabolic Hormones

Adrenal glands simultaneously secrete cortisol and protective hormones, such as DHEA and aldosterone. In young adults, secretion of both cortisol and its protective hormone DHEA by the adrenal glands are similar – approximately 20 mg per day for women and 30 mg per day for men. Whenever increased amounts of cortisol are secreted, healthy adrenal glands also release proportionately more DHEA and other adrenal hormones.

In many medical offices, cortisol or one of its derivatives are generally prescribed alone without protective anabolic hormones. This imbalanced treatment produces a number of side effects – mostly tissue atrophy – as shown in Table 5. To avoid these undesirable catabolic effects, DHEA and other anabolic hormones such as testosterone, female hormones, and possibly even growth hormone should

**Table 5. Glucocorticoid Excess**

Symptoms	Overdose Physical signs	Imbalance Physical signs due to DHEA and other anabolic hormone deficiencies	Adrenal suppression Symptoms and physical signs of increased cortisol deficiency after interruption of cortisol treatment
<ul style="list-style-type: none"> <li>• Euphoria</li> <li>• Agitation</li> <li>• Sleep disorder</li> <li>• Heart-pounding</li> </ul>	<ul style="list-style-type: none"> <li>• Swollen, balloon-shaped face</li> <li>• Buffalo neck (fat mass at the back and base of the neck)</li> <li>• Weight gain</li> <li>• Upper-body obesity</li> </ul>	<ul style="list-style-type: none"> <li>• Ulcers</li> <li>• Skin thinning, muscle loss</li> <li>• Bruising</li> <li>• Osteoporosis</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of energy</li> <li>• Loss of consciousness</li> <li>• Low blood pressure</li> <li>• Immune suppression</li> </ul>

be systematically administered (if the patient is deficient in these hormones), whenever hydrocortisone or one of its derivatives is prescribed.

### Intolerance to Cortisol

A minority of cortisol-deficient patients, usually those with the weakest adrenals, does not tolerate oral intake of cortisol. They may experience unbearable stomach acidity that can be overcome by enrobing the cortisol in a protective coat (a supplementary layer at the outside of the pill). Enteric coating protects the stomach against the pills' acidity by dissolving in the small intestine rather than in the stomach.

Patients may also feel weird, overwhelmed by a general malaise that spreads over the body with feelings of fainting and great weakness, when taking oral hydrocortisone or one of its synthetic derivatives. These patients find that cortisol therapy aggravates their cortisol deficiency symptoms. The usual cause is aldosterone deficiency induced or aggravated by glucocorticoid-induced reduction of pituitary secretion of ACTH, the hormone that stimulates secretion of all major hormones of the adrenal cortex. Aldosterone is another hormone secreted by the adrenal cortex. It keeps the blood pressure up. Treatment of aldosterone deficiency and its associated feeling of empty-headedness consists of adding fludrocortisone, the synthetic derivative of aldosterone.

A tiny minority of cortisol-deficient patients may still not tolerate or do well with cortisol, despite their desperate need for it. These cortisol-intolerant patients often experience all types of allergic or intolerance reactions to whatever medication they take. Their cortisol levels in blood and urine are usually dramatically low. Physicians may get headaches from trying to find strategies that could solve the problem.

Two alternate routes of administration may provide relief. Subcutaneous injections of cortisol at 30 to 50 mg a day may help, as may the application of 4–6 g/day of a liposomal gel with 5% cortisol applied to the buttocks, back, and belly in a very thin layer to avoid skin atrophy. A liposomal gel offers the best penetration of the body. If the applied layer is thin and if the patient rubs it ten times over

a large surface, it should penetrate quickly, leaving the skin intact. I tried these two forms, and they provided the same efficacy as my daily 30 mg/day of hydrocortisone intake.

### How to Make Cortisol Treatment Safe

First of all, **avoid excess**. Doses of 15–30 mg per day of hydrocortisone in women and 20–35 mg per day in men are usually physiologically safe<sup>28-31</sup> but may need to be reduced for smaller individuals. High cortisol doses should only be administered for a limited time in exceptional crises – to rescue a patient or an organ, for example – but always with concomitant anabolic hormone treatment.

The best method is to inform patients of cortisol excess signs and recommend they reduce the dose by 25 to 50% if there are ever signs of cortisol excess, such as a swollen face, weight gain, high blood pressure, or excessive agitation.

Second, **administer simultaneously protective anabolic hormones**. DHEA is the number one anabolic hormone that neutralizes excessive catabolic effects of cortisol associated with cortisol

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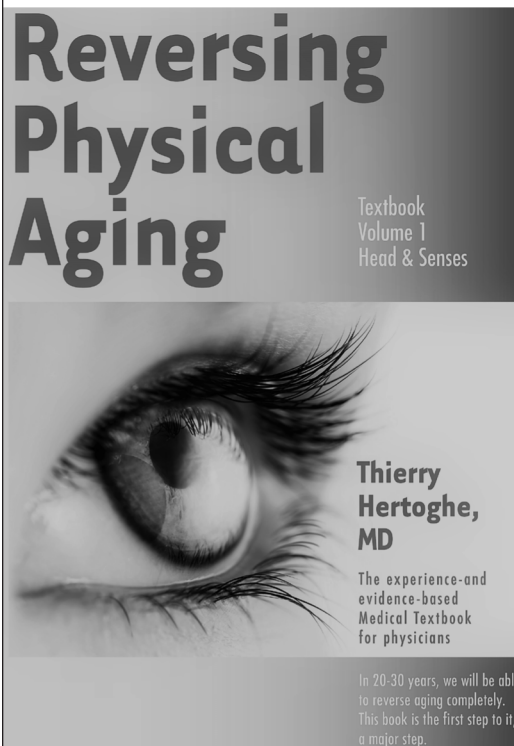
treatment.<sup>35-39</sup>

Young adult adrenals secrete DHEA and other anabolic hormones concomitantly with cortisol. Because DHEA is anabolic and builds up tissue, its presence blocks the excessive catabolic effects of cortisol. Cortisol is predominantly catabolic because it hastens catabolism to eliminate excessive tissue and unblocks energy by breaking glycogen down into glucose.

Both catabolism and anabolism are essential for health, but they must be appropriately balanced. To do so, both cortisol and anabolic hormones, such as DHEA, should be given in equivalent doses. Physicians should therefore mimic nature and provide DHEA with cortisol to avoid tissue wasting.

With aging, the production of DHEA declines considerably more than that of cortisol, resulting in an imbalance that favors catabolism above anabolism, which explains the progressive acceleration of aging in individuals past the age of 45. ➤

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➤ The third way to make cortisol treatment safe is to **avoid consuming “bad” carbohydrates**. In my experience, intake of sweet foods and cereals (that were not sprouted (such as traditional bread, pasta, muesli, porridge, etc.)), tend to block the major beneficial effects of glucocorticoid treatment and to increase the occurrence and intensity of undesirable side effects, especially swelling and weight gain. Thus, patients should avoid bad carbs in their diet at least five days a week. A protein-rich diet (180 g/day or more of meat, fish, and poultry) is also protective against excess glucocorticoid catabolism.

### Follow-Up

Follow-ups are mainly based on clinical assessments. More than for other hormone therapies, follow-ups of cortisol treatments should be done clinically for the most part, assessing for the presence of complaints and signs and avoiding any overdose signs.

Please note that saliva, serum, and 24-hour urine laboratory tests usually provide inconsistent results for follow-ups of bioidentical hydrocortisone and cortisone treatments. They are unstable and unreliable.

If hydrocortisone treatment is taken 30 minutes to three hours before blood and saliva tests, abnormally high free (and total) cortisol levels can be found in the serum due to peak levels of cortisol after absorption.

If hydrocortisone treatment at physiological doses is taken much later – seven to 24 hours after blood and saliva tests – cortisol levels usually drop back to their initial levels (from before treatment) or even to a supplementary

20-30% lower concentration (usually not more) because of transient and partial inhibition of the adrenal cortisol secretion.

In blood and saliva, cortisol levels are not stable during treatment. Not only is there a cortisol circadian rhythm, which makes cortisol levels fluctuate, with two to three times higher cortisol levels in the early morning than in late afternoon, but orally ingested cortisol does not bind strongly to cortisol-binding globulin (CBG), so the cortisol, which penetrates into the blood or saliva, quickly leaves for the target cells, decreasing cortisol levels.

The 24-hour urine test is not good for follow-ups either because it can show abnormally high levels of cortisol due to peak cortisol absorption with increased losses in urine, as well as unusually high excretion rates of cortisol metabolites (17-hydroxysteroids), even if cortisol treatment is adequate or insufficient. After intestinal absorption, the cortisol passes into the liver. Much of the cortisol is then broken down in the liver into inactive metabolites, which pass into the blood and then the urine, not reflecting real cortisol metabolic activity. The 24-hour urine is a must to control the reduction in adrenal androgens when dexamethasone is given to reduce body hair growth.

For non-bioidentical glucocorticoids, laboratory tests are even more inadequate for follow-up. None of the traditional laboratory tests can measure these synthetic glucocorticoids because of their different molecular structures. They might have some value to check the grade of adrenal suppression they may cause. Finding undetectable or nearly undetectable endogenous cortisol levels and very low metabolite levels in urine tests indicates that endogenous cortisol

secretion by adrenal glands might be excessively suppressed by treatment, possibly by overdose.

### Conclusion

Adrenal deficiency, particularly cortisol deficiency, is one of the most underestimated and misdiagnosed hormone deficiencies.

Untreated cortisol deficiency severely affects a patient's quality of life and brings a long road of unnecessary suffering. The hormone cortisol makes most stress bearable and considerably reduces suffering. Patients who remain in cortisol deficiency suffer excessively and continue to do so throughout their lives – the more severe the deficiency, the more suffering there is.

Many physicians and laypeople are reluctant to prescribe or take supplements of cortisol or one of its derivatives because of the unacceptable side effects of pharmacological doses of cortisol. These fears should not prevent physicians from treating cortisol-deficient patients with small, well-adjusted physiological doses of cortisol that are balanced with a protective DHEA supplement.

To correct a cortisol deficiency, the first things to do are to improve the environment, the lifestyle, and the diet. Let patients expose themselves to daylight and intense indoor light more. Recommend that they avoid pollutants – most pollutants are indoors. Regularly meditating or relaxing may also help increase cortisol levels when supplementary amounts are necessary. Avoiding unnecessary stress preserves cortisol stores from spillage. In addition, increasing the intake of protein- and fat-rich foods and avoiding sweets and cereals may also noticeably improve cortisol levels. In a minority of cases, these interventions may suffice.

In all other cases where cortisol treatment must be installed, these interventions optimize treatment results.



Born in Antwerp, Belgium, Dr. Hertoghe practices his medicine in his clinic in Brussels. With his sister, Dr. Thérèse Hertoghe, they proudly represent the fourth successive generation of physicians working with hormonal treatments – and this since 1892 (after Eugène Hertoghe, former vice president of the Royal Academy of Medicine in Belgium, and Luc and Jacques Hertoghe, endocrinologists). Dr. Thierry Hertoghe devotes his life to the promotion of a better, patient-oriented, and evidence-based medicine.

Author of numerous books, Dr. Thierry Hertoghe also travels a lot to take part in numerous conferences and congresses throughout the world. He co-organizes many of these specialized gatherings and holds important positions in several international and national medical organizations (which usually tend to fight against aging). He is the president of the International Hormone Society (over 2500 physicians), and of the World Society of Anti-Aging Medicine (over 7000 physicians), as well as the supervisor of two important postacademic trainings for doctors.

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**There are 461 references. Please see the digital version of the article on our website in the January and Feb/March 2018 issues for the complete reference list.**