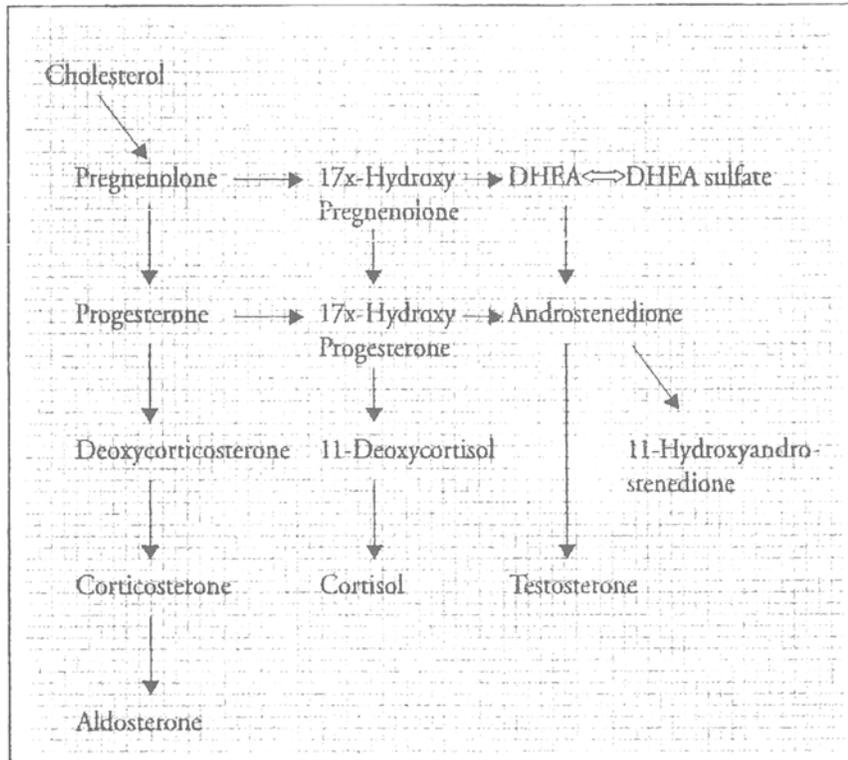


# IMPLICATIONS OF ADRENAL INSUFFICIENCY

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**A** nutritional program that does not address adrenal insufficiency issues may eventually fail. Physicians and other healthcare practitioners often misdiagnose adrenal insufficiency. In this article, we will discuss the signs, symptoms, etiologies, diagnosis, and possible treatments from both a conventional and complementary perspective.

## DEFINING THE ADRENALS

The adrenal glands are paired structures that are located retroperitoneally at the upper pole of each kidney. Two distinct regions of this organ are noted. The golden yellow outer portion of the gland is the adrenal cortex, and the inner portion is called the medulla. Above is a schematic of the hormones produced by the adrenal cortex.

The functions of the medulla and cortex are distinctly different. The cortex is responsible for the production of four major hormones. The primary one is cortisol, a glucocorticoid involved in multiple biological processes, including glucose control; carbohydrate, fat, and protein metabolism; inflammatory regulation; intestinal and colon membrane repair; and the stress response. The second, aldosterone, a mineral-corticoid, is directly involved in the renin-angiotensin-aldosterone feedback loop that regulates renal potassium excretion while preserving sodium by re-absorption. Third, this important structure produces dehydroepiandrosterone (DHEA), DHEA is a well-known sex hormone precursor and immune system enhancer. Finally, pregnenolone is also produced in this area. Pregnenolone is a precursor to DHEA, with a predilection to cascade down to progesterone.<sup>1</sup>

The medulla portion of the adrenal gland is primarily involved in the secretion of norepinephrine and epinephrine (adrenaline). This is the area that is responsible for preparing the body for the "fight-or-flight" response. These hormones can set the tone of the adrenergic (sympathetic) nervous system.<sup>2</sup> Hypertonicity of the sympathetic nervous system increases the heart rate, raises blood pressure and blood sugar levels, and dilates the eyes and bronchial tubules.

### **ADRENAL DISORDERS**

Primary adrenal cortical generalized disorders (those related directly to the gland) may be divided into four categories. Milder degrees of adrenal insufficiency lack the classic features of Addison's disease. In "low adrenal reserve," the mildest form, the adrenals can still produce sufficient hormones to maintain an apparently normal state of health in the absence of significant stress. However, when stressful conditions increase the demand for adrenocortical hormone, symptoms ranging from fatigue to complete collapse may occur. Many conditions are linked to psychological stress, such as angina, asthma, autoimmune diseases, adult diabetes mellitus, colds, hypertension, and menstrual irregularities. Add to these the ailments noted earlier, and it is easy to see that many different health problems influence overall adrenal function.<sup>3</sup> Many practitioners encounter, on a daily basis, patients with this type of relative adrenal insufficiency as opposed to overt failure. There is no clear-cut presentation of patients with adrenal fatigue issues. The four primary adrenal deficiencies are:

1. Addison's disease, a failure of the adrenal cortex, is often caused by autoimmune phenomenon, tuberculosis, metastatic carcinoma, lymphoma, hemorrhage, fungal infection, sarcoidosis, and hematomacrosis. A drop in IgA can increase intestinal permeability. In turn, that may exacerbate or cause autoimmune diseases, eventually leading to cortisol depletion.<sup>4</sup> A decrease in IgA would allow for a translocation of bacteria into the bloodstream, which in turn would stimulate interleukin release. This would then stimulate the hypothalamic-pituitary-adrenal (HPA) axis, which would lead to a further demand for cortisol, eventually causing a relative deficiency.

2. Other causes of adrenal insufficiency are hereditary, congenitally acquired, vascular spasm, degeneration, traumatic and chemical, nutritional deficiencies, and electromagnetic energy fields. Aliphatic compounds cause necrosis of the zona fasciculata and zona reticularis where the glucocorticoids are produced. Organic chlorine compounds and carbonates have caused histological changes to these areas in animal models. Dioxins and fire ant poison directly suppress glucocorticoid synthesis, resulting in hypoglycemia.<sup>5,6</sup>

Other chemicals implicated in adrenal insufficiency include tobacco, alcohol, street drugs, heavy metals, sugar, coffee, pollution, pesticides, herbicides, and fungicides. White flour can also cause these problems. According to Seyle, the difference between whether or not stress is harmful depends upon the "strength of the system."<sup>7</sup> This is related not only to adrenal reserve, but also to the closely related issue of dietary intake. Refined carbohydrates (e.g., sugar and white flour) tax the

body's nutritional reserves. While contributing very few of the nutrients required for their metabolism, they deplete a great deal of the nutrients also necessary for adrenal support, especially B vitamins.<sup>8</sup>

The authors also believe that extremely low-frequency electromagnetic fields from computers, hair dryers, airplanes, and electric blankets, can damage this vital tissue.<sup>9-10</sup>

### SECONDARY DISORDERS

Secondary disorders can also cause adrenal cortical deficiency. These include nonsteroidal anti-inflammatory drugs and pituitary disease, which are unrelated to the adrenal gland itself. Even oversecretions of the medulla can affect cortical function. A stressor creating a “fight-or-flight” response releases adrenaline.

**Note:** “Stress” is defined in a physiological context as any factor that acts to destroy homeostasis. More precisely, it is the body’s response to any factors that threaten its ability to maintain homeostasis.<sup>34</sup>

Adrenaline release also causes liver glycogen stores to free glucose. In addition, the hypothalamic/pituitary axis is stimulated, as ACTH and beta endorphin are released. Finally, the adrenal gland increases cortisol output and decreases DHEA production. This cascade will affect sex hormone production by decreasing testosterone and estrogen.

For many women, the transitional stage of life leading to menopause is fraught with unacceptable and well known symptoms, caused by decreased ovarian hormone production. In a healthy woman, the adrenal glands take over hormonal production to some degree. Many women, however, approach menopause in a state of chronic emotional and nutritional depletion, which affects optimal adrenal function.<sup>35,36</sup> A secondary side effect of this stress response is decreased mental clarity due to the hippocampus’s chronic exposure to cortisol.<sup>37</sup>

The father of modern stress research, Hans Selye, described the stress response as a part of the larger “general adaptational syndrome.” This syndrome is composed of three phases:

- Alarm
- Resistance
- Exhaustion

Reactions in the brain trigger the alarm reaction, also known as the fight-or-flight response. These reactions ultimately cause the pituitary to release ACTH, which in turn causes the adrenals to release stress-related hormones, such as adrenaline. This short-lived phase is followed by the resistance phase, which allows the system to continue its adaptation to stress long after the alarm phase effects have worn off. Corticosteroids, such as cortisol, mediate this response. However, if prolonged, stress reaches the final phase, which is exhaustion.<sup>38,39</sup>

3. Bilateral adrenalectomy refers to the removal of both adrenal glands.
4. Adrenal enzyme deficiency is the other disorder of the adrenal cortex that can lead to primary adrenal cortex insufficiency.<sup>11</sup>

### **INTEGRATIVE TREATMENT PROTOCOL**

If the patient exhibits decreased levels of cortisol at all examinations, clinical repletion with hydrocortisone (possesses both glucocorticoid and mineralocorticoid activity) is usually effective. Results are quick and reliable, According to the work of William M. Jeffries, cortisol, when properly

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administered, is as safe as any other naturally produced hormone. The ill-informed use of higher pharmacologic doses, with their devastating side effects, has engendered an unwarranted degree of caution when addressing cases of documented adrenocortical hypofunction. The evidence supports the use of physiologic sub-replacement doses (5mg or less q.i.d.) in these patients. Low doses result in neither hypercortisonism, nor significantly impaired resistance to stress.<sup>12</sup> The rationale here is similar to that seen with

inappropriate dosing of human growth hormone (HGH), which may cause acromegaly. However, this does not preclude the prudent use of physiologic doses.

Using herbal and other nutraceuticals (e.g., vitamins, minerals, and amino acids) does not seem to afford the clinician with the control nor the response needed in these severely depressed individuals. We recommend prescribing a three-month supply of hydrocortisone and carefully monitoring the patient with regular monthly visits. After 90 days, add one or two of the nutraceuticals listed under "Specific recommendations" (right). Then gradually reduce and eliminate the hydrocortisone over a 2-week to 30-day period. If the gland is still not operating appropriately, further drug repletion may be necessary. Certain individuals may require hydrocortisone on a life-long basis. If you are going to stop the use of corticosteroids, it is best to taper the drug so as not to create a frank adrenal failure. Although this would be unusual in such low doses, it is best to reduce the dose in half for one week, and then half again for another week, and then stop.

### **SYMPTOMS OF ADRENAL INSUFFICIENCY**

The most common presenting symptoms of chronic primary adrenal cortical insufficiency are weakness, fatigue, weight loss, and anorexia. Low blood pressure, salt cravings, gastrointestinal symptoms, and hyperpigmentation can also be seen in these patients, Non-specific symptoms are commonly seen in marginally deficient patients. These may include poor mental clarity, decreased sexual function, decreased libido, and just not "feeling right:"

## SPECIFIC RECOMMENDATIONS

1. If DHEA levels are low, replacement is required. Normal ranges for salivary levels are 3-10 ng/ml, with 8-10 ng/ml reflecting the best immune function. Typically, patients with chronic diseases exhibit low or below-normal levels, both of which should be treated aggressively. In the absence of frank adrenal failure, we have found that rheumatoid arthritis, fibromyalgia, and even polyneuropathy will usually respond to DHEA rather than other drugs."

2. All patients should be encouraged to.:

- a. Stop smoking;
- b. Discontinue any street drugs;
- c. Decrease alcohol consumption;
- d. Decrease intake of fats, salt, and sugar;<sup>14</sup>
- e. Decrease caffeine consumption,
- f. Exercise aerobically at least three hours a week;
- g. Use stress-reduction techniques such as prayer, meditation, soothing music, funny movies,
- h. guided imagery, or biofeedback<sup>15</sup>
- i. Get professional help to deal with anger and rage, and deal with psychospiritual issues that surround work, family, care-giving, self-esteem, and body image, which may help reduce cortisol levels; and
- j. Limit exposure to extremely low-frequency magnetic energy fields.

3. If secretory IgA levels are low, repair the probable intestinal permeability with L-glutamine, an amino acid often taken from lung and bone to replenish the supply for the enterocytes and colonocytes. Also, immunoglobulin repletion with a whey product high in immunoglobulin IgA, or the inclusion of eggs in the diet, may be helpful. Melatonin has also been shown to improve secretory IgA.<sup>16</sup>

4. Based on our observations, we recommend an optimal ratio of omega-3 and omega-6 oils (4: 1).

5. Suggest increasing intake of pantothenic acid (vitamin B<sub>5</sub>). Eating more whole grains and eggs will increase this vital nutrients.<sup>17</sup>

6. Recommend 2-5 grams of potassium a day.<sup>18</sup>

7. Vitamins C (1,000-2,000mg/day) and B<sub>6</sub> (100-300mg/day) are vital nutrients for adrenal function.

8. Zinc (50mg/day) and magnesium (500mg/day) are recommended.<sup>19</sup>

9. The herb ashwagandha may be helpful. Several adaptogens, such as ginseng (Panax equals Korean/Chinese), provide tonic effects.<sup>20</sup> Make sure that this adaptogen contains 25-50mg of ginsenosides in daily divided doses. This usually translates to 1-2 grams per day. Ginseng has been shown to amplify the glandular effects. It does this by increasing the responsiveness of the adrenal gland and the ability to control the gland secretion. Use short, 90-day courses of ginseng, and alternate this with licorice derivatives.

10. Licorice has aldosterone-like properties.<sup>21</sup> It can be helpful in adrenal corticoid abnormalities. Glycyrrhetic acid is a pentacyclic triterpene derivative of the b-amine type. This substance also exhibits regulatory action on the adrenal gland.<sup>22</sup>

11. Soluble adrenal fractions, a nutraceutical, can stimulate a sluggish gland to become more productive. Increase this product until there are symptoms of nervousness or difficulty sleeping. Then reduce the dose slightly until there are no more undesirable side effects.

12. Individuals in a chronic stress state often have an increase in their phenylalanine-tyrosine ratio. Both tyrosine and phenylalanine restore epinephrine levels.<sup>23</sup> Multiple studies have documented beneficial results in fatigue and depression by using supplemental phenylalanine or tyrosine. Phenylalanine is decarboxylated to phenylethylamine (PEA), which has amphetamine-like stimulant

properties (found in high concentrations in chocolate). Phenylalanine is also hydroxylated to tyrosine, which eventually forms epinephrine. However, its primary supplemental effects are thought to be through the former pathway. Tyrosine, which is necessary for the formation of norepinephrine, is found at low levels in depressed patients. Supplementation increases levels of 3-methoxy-4-hydroxyphenethylene glycol (MHPG) in the urine. This is probably the principle breakdown product of norepinephrine in the central nervous system (CNS), and may provide a marker to determine which amino acid to supplement.<sup>24,25</sup>

13. Check patients for heavy metal intoxication. Remove any heavy metal burdens with an appropriate chelating agent.<sup>26,27</sup>

14. Coenzyme Q10, and two digestive enzymes.<sup>28</sup>

15. Desiccated adrenals can be used for a short time.<sup>29</sup>

16. Vitamin A may help correct abnormal exhaustion.<sup>30</sup>

### SUMMARY

The clinician's lack of response to compromised adrenal function can have deleterious effects on the patient. You will find that your nutritional program falls short of your goals. In less-than-severe adrenal insufficiency (adaptive phases vs. maladaptation), add the nutrients described. Monitor your success by repeating the salivary testing every 90 days until the situation is corrected. If your regimen fails, consider the following possibilities:

1. Your dosage was too low.

2. Your length of treatment intervals before retesting were too short.

3. Patient compliance was poor. Make sure the patient is taking the prescribed dosage.

4. External causes were not eliminated.

5. IgA levels did not improve.

6. If the patient was not responding well to the supplements he or she was taking, make sure the supplements come from a company that uses pharmaceutical-grade nutrients.

7. Conventional treatment and/or nutraceuticals did not effectively address underlying disease pathology.

8. Patient's medications were hindering an optimal result.

9. Chronic anxiety and/or depression were not adequately treated.

10. Food allergies had a negative effect on result. For example, when IgA is low, foreign substances, including incompletely digested bits of food, can enter the circulation and become antigens.<sup>31,32</sup>

11. Bioavailability should also be considered in treatment evaluation. For example, does the patient have adequate hydrochloric acid for the initial dissolution of the prescribed product? Is gut dysbiosis preventing appropriate absorption?

If all the above possibilities have been explored and the patient is still not responding well, try a short course of hydrocortisone and note the effect. A measurement of plasma renin activity can help you assess the need for mineral corticoid replacement therapy. The clinician should measure blood pressure using a tilt table, if not available, test the patients blood pressure, in both arms, in lying, sitting, and standing positions. Patients may require the addition of fludrocortisone, a mineralocorticoid.<sup>33</sup>

## DIAGNOSING ADRENAL INSUFFICIENCY

The practitioner must correlate the history presented with the physical examination. When adrenal insufficiency is suspected, the following workup might be necessary.

Serial saliva testing is the easiest and most convenient way to diagnose adrenal cortical deficiency. Patients are sent home with a simple kit. Early morning noon, dinner, and PM samples are obtained by soaking a cotton ball with saliva. Lab results of this test can give accurate information about cortisol levels, DHEA, anti-gliadin antibodies, and secretory IgA. The salivary ACTH test has been shown to be 1,000 times more sensitive than serum testing.<sup>40</sup> This type of serial evaluation is necessary, considering the fact that secretion of adrenocorticotropin and subsequent corticotropin-releasing hormone (CRF) are pulsatile and manifest diurnal circadian rhythm.<sup>41,42</sup> Utilizing the results of this test makes it easier to develop the best treatment strategy. Consider asking the lab to do a 24-hour urinary excretion for 17-hydroxycortical steroids.

If done conventionally, adrenal responsiveness can be determined at any time of day. However, it is possible that milder degrees of low adrenal reserve may not be detected unless ACTH tests are performed in the morning, at the time when plasma cortisol levels are the highest. The best conventional screening test is to measure a serum cortisol before, and 30-60 minutes after, an IV or IM injection of 0.25mg synthetic ACTH. A normal response would be a rise in the serum cortisol level of two to three times baseline, or a peak response no less than 15mcg/ 100ml.<sup>43,44</sup>

## CONCLUSION

Careful examination of the chronically ill patient often reveals significant adrenal insufficiency. The system cannot support adequate immune function without hormonal health. Use of supplemental hormones may be necessary.

Practitioners with the appropriate license and knowledge can join your health team. Combining conventional and complementary approaches will give your patients the proper support they need, and reward you with a profound sense of accomplishment.

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