

## **SAFE USES OF CORTISOL**

This book is the ultimate reference on cortisol by Dr. William McK. Jefferies. It can be purchased directly from the publisher.

### **Charles C Thomas Publisher Ltd.**

2600 First Street Springfield, Illinois 62704 (800) 258-8980  
www.ccthomas.com

**SAFE USES OF CORTISOL** By William McK. Jefferies  
Published 2004 (3rd edition) 232 pp., 6.75 x 9.75, 10 il.

<b>ISBN</b>	<b>TYPE</b>	<b>PRICE</b>
978-0-398-07500-2	Hard	\$63.95
978-0-398-07501-9	Paper	\$43.95

### **DESCRIPTION**

The Third Edition of this popular book brings up to date the material that so many readers found helpful in the previous editions. The text has been revised and reorganized with current chapters focusing on the history of cortisol use, sources of confusion regarding cortisol therapy, the significance of normal adrenocortical function, generally accepted uses of physiological dosage, viral infections, miscellaneous clinical conditions, and future directions for research and therapy. The author provides explanation and confirmation of the rationale for the effectiveness and safety of the uses of physiological dosages of cortisol in the treatment, not only of patients with rheumatoid arthritis and other autoimmune disorders, but also of patients with chronic allergies, chronic fatigue syndrome, gonadal dysfunction, infertility, shingles, acne, hirsutism, respiratory infections, and other less

## Chapter 4

# GENERALLY ACCEPTED USES OF PHYSIOLOGIC DOSAGES INCLUDING THE DIAGNOSIS AND TREATMENT OF MILD ADRENOCORTICAL DEFICIENCY

### ADRENAL INSUFFICIENCY

The most logical use of physiologic dosages of cortisol is in the treatment of patients with known adrenal insufficiency. Severe examples of this disorder are manifested by hyperpigmentation of the skin, weakness, fatigue, anorexia, and susceptibility to collapse and shock with exposure to stress. This clinical picture was first described by Sir Thomas Addison in 1855 and subsequently has been called Addison's disease. For many years tuberculosis of the adrenals was its most frequent cause, but with the decreased incidence of tuberculosis resulting from improved prevention and treatment, "idiopathic" adrenal insufficiency or adrenal insufficiency resulting from an autoimmune phenomenon<sup>1</sup> have become more common diagnoses.

These are relatively rare disorders, however, and when cortisone and adrenocorticotrophic hormone (ACTH) became available for human use in 1948, these hormones first attracted worldwide attention by their dramatic beneficial effects on patients with rheumatoid arthritis. The dosages employed were large, however, and when continued they produced undesirable and sometimes catastrophic side effects, so this treatment developed a reputation for being too dangerous for general use in patients with rheumatoid arthritis and other autoimmune disorders. This reputation has apparently caused a tendency to minimize the size of replacement dosages of steroids for patients with adrenocortical deficiency that are recommended in endocrine textbooks and sometimes even a preference for synthetic steroids over the natural hormone, cortisol.

Our rationale for the treatment of patients with adrenocortical deficiency has been based on the impression that nature usually has good reasons for choosing the specific chemical substances secreted as hormones, and the studies illustrated in Figures 1 and 2 (pages 15 and 16) provide information indicating that a total dosage of 35 to 40 mg of cortisol daily

administered in divided doses at maximum intervals of 8 hours should supply adequate glucocorticoid replacement for an unstressed adrenalectomized patient. Because patients with spontaneous adrenocortical deficiency usually seek medical care before a complete lack of cortisol develops, replacement dosages for such patients usually total less than 35 mg daily, taken as 7.5, 5, or 2.5 mg four times daily before meals and at bedtime (ac and hs). Supplementary sodium-retaining effect in the form of 9 alpha-fluorohydrocortisone (9 alpha-FF [Florinef®]), 0.1 mg daily or three times weekly, is rarely needed except in totally adrenalectomized patients.

Meanwhile, experience with the use of small, safe, physiologic dosages of cortisone or cortisol in patients with ovarian dysfunction and infertility revealed that patients with associated allergies, chronic fatigue or autoimmune disorders also reported improvement in these conditions while taking the steroid, without experiencing any undesirable side effects. These results were published in a leading medical journal,<sup>2</sup> but the reputation of glucocorticoids had become so bad that they received little attention. Subsequently, improved methods of diagnosis have enabled the identification of mild degrees of adrenocortical deficiency, thus providing an explanation for at least some of these beneficial effects.

Hence, the diagnosis and treatment of mild adrenocortical deficiency, a condition that is rarely mentioned in medical textbooks, has become important for all practicing physicians to recognize. It may be primary, resulting from inadequate production of cortisol by the adrenals and sometimes termed "low adrenal reserve," or it may be secondary to inadequate stimulation of the adrenals by adrenocorticotrophic hormone (ACTH) from the pituitary or by corticotropin releasing factor (CRF) from the hypothalamus. Another possible cause of symptoms of cortisol deficiency is a defect in the cellular receptors for cortisol causing associated normal or elevated levels of plasma cortisol. A similar type of resistance to thyroid hormone that improved with administration of physiologic dosages of cortisol is described in Chapter 10. The recognition and treatment of these disorders is discussed in the chapters and sections devoted to them, but tests to determine the integrity of the hypothalamus-pituitary-adrenal (HPA) axis and general principles of treatment will be discussed at this time, since they apply to all disorders of adrenocortical function, whether primary or secondary, complete or partial. The causes for these disorders are largely unknown, but they are often related to stress and inherited predisposing factors.

The symptoms and signs of severe adrenocortical deficiency are well described in standard medical or endocrine textbooks, but mild adrenocortical deficiency has received little attention. When patients with rheumatoid arthritis or with other conditions that were later identified as autoimmune disorders were found to improve dramatically with administration of large dosages of ACTH or glucocorticoids, the possibility that they might have adrenal deficiency was considered, but because they did not have the characteristic features or laboratory findings of hypopituitarism or of Addison's disease, this possibility was eventually apparently forgotten even though at least some had abnormal levels of excretion of steroids in their urine. Recent reports have presented evidence that patients with rheumatoid arthritis and several other autoimmune disorders have abnormal responses of their HPA axes to stress, so the possibility that the development of these disorders might be related to defective HPA responses seems likely. This would explain the beneficial effects of small, physiologic dosages of cortisol that have been observed in some of these patients and support the advisability of testing the integrity of this axis and the use of therapeutic trials with safe, physiologic dosages of cortisol in patients with these disorders. Many patients with chronic allergies, another condition that improves with large dosages of ACTH or glucocorticoids, also have been found to have evidence of mild adrenocortical deficiency. These findings will be discussed in more detail in subsequent chapters, and they emphasize the importance of testing for the possibility of deficient adrenocortical function, either primary or secondary, in patients with these conditions.

Because chronic fatigue is frequently the earliest symptom of mild adrenal insufficiency, and with the availability of a simple method of determining adrenal responsiveness to ACTH, patients coming to our clinic complaining of chronic fatigue without other evident cause such as inadequate rest, anemia, hypothyroidism, or chronic illness of any type have been given ACTH tests in addition to having determinations of baseline levels of plasma cortisol and of plasma ACTH. Initially, commercial preparations of ACTH were used for the tests, but subsequently Cortrosyn® (Organon), an active ACTH fraction consisting of the first 24 of the 39 amino acids of natural ACTH, which has a relatively rapid effect enabling the test to be run in 30 minutes and is less apt to cause sensitivity reactions, has largely replaced ACTH for the tests.

It is preferable to have these tests run in the morning after the patient has had adequate sleep and has not taken for a sufficient interval of time

any glucocorticoid or other medication that might affect adrenal function or blood levels of cortisol, but helpful information can be obtained by running them at any time of day. A more sensitive low dose Cortrosyn test has been suggested for the diagnosis of mild adrenal deficiency,<sup>3</sup> but because therapeutic trials are usually justified, even in patients with apparently normal tests, sometimes it is preferable to delay further testing until a therapeutic trial has been made, especially if it might avoid otherwise unnecessary hospitalization.

It is important to be aware that test results that fall within the "normal range" do not rule out the possibility that a patient might have mild adrenal deficiency since the normal range was probably obtained from a group of people who did not have classical Addison's disease or hypopituitarism or any other known physical disorder and is rather broad. Hence, it might include persons with chronic allergies or other conditions that may be associated with mild adrenocortical deficiency. Furthermore, as previously mentioned, mild adrenal deficiency can occur secondary to inadequate stimulation by ACTH from the pituitary or by CRF from the hypothalamus. These patients may have low normal baseline blood cortisol levels that respond normally to Cortrosyn, but still improve with a physiologic dosage of cortisol. Hence results of Cortrosyn tests within the normal range do not exclude the possibility that patients might benefit from cortisol therapy, so a therapeutic trial might still be justified.

Patients with secondary adrenocortical deficiency may need to have x-rays of the sella turcica and determinations of blood growth hormone (GH), thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH) levels because of the possibility that they might have a tumor or other lesion in this area, but most patients with this disorder do not seem to have identifiable organic lesions. Other studies that might be helpful include a complete blood count with differential, blood sedimentation rate and tuberculin test because of the possibility of an infectious process, and x-rays of the adrenal areas and chest.

For a *Cortrosyn test*, blood is drawn for baseline plasma cortisol and ACTH levels, recording the time of day. As mentioned above, although it is preferable to perform the test in the morning when plasma cortisol levels are highest if the patient is on a normal sleep-wake schedule, adrenal responsiveness can be determined at any time of the day. The patient does not have to be fasting, although this is also preferable, but he or she should not have taken any glucocorticoid for at least 12 hours,

and preferably not for several weeks, because an abnormal Cortrosyn test due to low adrenal reserve may return to normal after a short course of cortisone acetate or cortisol or probably of any other glucocorticoid, and evidence of low reserve may not return until medication has not been taken for a month or longer. After the blood for baseline cortisol and ACTH is drawn, the patient receives an injection of 25 units of Cortrosyn into the deltoid muscle of the upper arm. Thirty minutes later a second blood specimen is drawn for plasma cortisol determination. The patient is then instructed to record any change in symptoms over the next 24 hours. A normal response is considered an increase in cortisol level to at least double the baseline value, but most normal persons will have an increase greater than twofold, and patients with secondary adrenocortical deficiency will often report a transient improvement in symptoms suggesting a mild deficiency in their production of ACTH. When plasma cortisols are determined by radioimmunoassay, as was done in our laboratory, baseline plasma cortisols are normally between 15 and 30 mcg/100 ml in the morning and between 5 and 15 mcg/100 ml in the afternoon.

This test is an example of the impossibility of having strict end points in designating normal ranges of hormone levels, especially for a dynamic hormone such as cortisol, whose levels may fluctuate from minute to minute depending upon the degree of stress in addition to diurnal variation. Hence, patients with adrenal insufficiency may have plasma cortisol levels within low normal range, especially in the afternoon and evening, and patients with hyperadrenalism may have plasma cortisol levels within upper normal range in the morning. It is therefore possible that milder degrees of low adrenal reserve may not be detected unless Cortrosyn tests are performed in the morning at a time when baseline cortisol levels are maximum. Furthermore, patients vary in their susceptibility to various degrees of stress, including the stress of having injections and blood tests, so these factors must be considered in interpreting the results of tests. Hence, a diagnosis of mild adrenocortical deficiency should depend primarily on the clinical picture and therapeutic trials are often justified even when the results of tests fall within the normal range.

It is also important to bear in mind that normal ranges for baseline levels of plasma cortisol have been determined by measurements on apparently normal subjects who had no clinical evidence of hyperadrenalism (Cushing's syndrome), hypoadrenalism (Addison's disease),

congenital adrenal hyperplasia (adrenogenital syndrome), or any other apparent illness. As is evident from subsequent discussion, adrenal dysfunction can be present in persons who do not fall into any of the above groups, hence so-called "normal" ranges are probably greater than those that would be obtained by excluding, for example, any subject with acne, hirsutism, or allergies, conditions that may have associated mild disorders of adrenocortical function. Adrenal insufficiency is also characterized by an elevated plasma ACTH level, but patients with low adrenal reserve and not under stress may have normal plasma ACTH, so the Cortrosyn test of adrenal response is a more sensitive method for diagnosing this disorder.

It should be emphasized that a "normal" baseline plasma cortisol and response to Cortrosyn does not rule out the possibility that a patient might improve with a physiologic dosage of cortisol, so for patients with disorders that suggest the possibility of mild adrenal deficiency, therapeutic trials with a small, subreplacement dosage of cortisol might still be helpful. Hence inability to obtain baseline cortisol and ACTH levels and Cortrosyn stimulation tests does not contraindicate therapeutic trials with physiologic dosages of cortisol in patients with disorders that might improve with such treatment, but the demonstration of deficiency provides a clear indication for treatment.

Cortisol, like adrenalin and insulin, is a very dynamic hormone whose production can vary from minute to minute, or even from second to second, depending upon the amount of stress being experienced. This stress may be physical, mental or emotional. In the unstressed state it is normally produced on a diurnal pattern depending upon a person's sleep-wake schedule, maximum production occurring about an hour after awakening in the morning, then slowly decreasing during the day, reaching a low point about an hour after retiring at night. Since the duration of effect on each dose of cortisol is a maximum of about 8 hours, an optimum replacement schedule would have a maximum interval of 8 hours, but for several reasons most patients prefer to take four doses daily, one before each meal and the fourth at bedtime.

Because spontaneous adrenal insufficiency results from progressive destruction of adrenal tissue, symptoms appear when the process reaches the point where remaining adrenal tissue is insufficient to maintain normal well-being. As mentioned earlier, this may require destruction of over 90 percent of the glandular tissue, but the remnant is capable of some function, so replacement dosages of cortisol in chronic adrenal

insufficiency are usually less than the 35–40 mg daily that are required for the totally adrenalectomized patient. Most patients can be maintained on between 20 and 30 mg daily in divided doses. Although some patients may feel well on less than 20 mg daily, it seems preferable to give at least this much cortisol, even to patients with low adrenal reserve, because it takes the strain off of the residual adrenal tissue and provides for more functional reserve in times of stress. Under some circumstances, it appears to provide an opportunity for residual tissue to regenerate. A few patients with low reserve have demonstrated evidence of recovery of reserve after months or even years of such treatment, but most seem to require some replacement for the remainder of their lives.

In patients with adrenal insufficiency secondary to tuberculosis, the administration of cortisol was initially employed with hesitation because of the well-known anti-inflammatory effect of large doses of glucocorticoids, causing a tendency for tubercles to break down and enable dissemination of the previously walled-off tubercle bacilli. Later, when it was found that the use of glucocorticoids in conjunction with antituberculous therapy actually enhances the effectiveness of the latter, the combined use of the two types of therapy became accepted practice. A patient with adrenal insufficiency secondary to tuberculous infection, therefore, should initially receive a suitable course of antituberculous therapy in addition to replacement cortisol in physiologic dosage.

A schedule of replacement glucocorticoid therapy in adrenal insufficiency employing two-thirds of the daily dosage before breakfast and one-third before supper has been widely recommended.<sup>4</sup> This is based upon the characteristic diurnal variation in plasma cortisol levels, with a peak shortly after waking in the morning and a low point shortly after retiring at night. Patients with adrenal insufficiency will do fairly well on this schedule, but when we have had them compare it with the same total dosage in four divided doses, they have invariably preferred the latter. This is not surprising in view of the evidence that the half-life of cortisol in the blood is only 100 minutes, and some metabolic effects of even large doses do not last longer than eight hours.<sup>5</sup> Furthermore, although plasma cortisol reaches its lowest level shortly after retiring in the evening, it begins to rise during sleep so that by the time the patient arises in the morning it is almost at its peak for the 24 hour period. Hence, instead of the twice daily dosage more closely imitating the natural diurnal pattern, it causes a peak level in the morning followed by a period of lower than normal levels in the afternoon, then a smaller



peak after supper followed by lower than normal levels during sleep and at the time of awakening in the morning. It is not surprising that a schedule employing four doses taken before meals and at bedtime produces more energy and less fatigue.

A four times daily schedule also seems to result in greater decrease in pigmentation in patients with this manifestation of adrenocortical deficiency. It is therefore possible that a schedule of only two doses daily in patients with more severe deficiency may not produce sufficient feedback to prevent excessive ACTH production, and this might contribute to the tendency for some patients on this program to develop pituitary adenomas (Nelson's syndrome).<sup>6</sup> Longer acting derivatives of cortisone or cortisol, such as prednisone or dexamethasone, on a once daily schedule, have therefore been suggested,<sup>4</sup> but because nature usually has a reason for using the hormones normally produced by the body, and because extensive experience with the normal hormones in physiologic dosages has confirmed their safety and effectiveness, it seems preferable to continue their use for treatment of patients with adrenocortical deficiency, either primary or secondary, complete or partial.

The taking of any medication every eight hours or four times daily might be considered too difficult for patients to follow, but this has not been a problem with patients with mild adrenal deficiency. Their subjective improvement has been sufficient to keep most patients taking their medication regularly. Taking cortisol three times daily, or even twice daily, will produce some improvement, but for optimum benefit the four times daily schedule has usually been more helpful and easier to follow. Patients working on night shifts or traveling to different time zones will need to adjust their schedules for taking their medication to their new mealtimes and bedtimes but when they do this promptly, they often report that this adjustment seems to diminish their tendency to develop travel fatigue or "jet lag."

Some patients report that cortisone acetate seems to be less apt to cause acid indigestion than cortisol, so if it is available, it may be tried, but since cortisone must be converted to cortisol before producing therapeutic effects, it is becoming less frequently used. Also, although a lower dosage at supper time is logical and seems to diminish a tendency to insomnia that occurs in some patients, a lower dosage at bedtime is not always desirable because with normal diurnal variation the plasma cortisol level rises during sleep to reach a peak shortly after awakening in the morning.

An undesirable effect of taking any dosage of glucocorticoid at bedtime is that it tends to cause persistent renal function during sleep, resulting in the need to get up and void once or twice during the night. This is not a serious problem, and most patients prefer this inconvenience to the morning fatigue that may result from an inadequate dose of steroid at bedtime. If the patient has sufficient adrenal reserve, the bedtime dosage may be decreased or omitted entirely without difficulty. The occasional patient who complains of inability to sleep after the bedtime dosage of glucocorticoid may be found to be taking it without milk or food, and the insomnia appears to be related to a tendency to acid indigestion aggravated by the steroid. Such a complaint can usually be corrected by taking an antacid or milk or other light nourishment at the time of the bedtime dosage.

Also, insomnia after the bedtime dosage may be related to an excessive intake of coffee or other caffeine-containing beverages that patients with chronic fatigue frequently resort to in an effort to obtain more energy. Patients with untreated or inadequately treated adrenal insufficiency seem to be tolerant of larger amounts of caffeine; hence, when suitable replacement dosages of cortisol are administered and their tolerance return towards normal, they may develop symptoms of excessive caffeine intake. It is, therefore, wise to caution patients who are starting on physiologic dosages of glucocorticoid regarding this possibility.

Patients with chronic adrenocortical deficiency can usually be well maintained with cortisol, 5 or 7.5 mg orally before each meal and at bedtime. If a patient has a peptic ulcer or predisposition to this disorder, antacid should be taken with each dose. If this is done, the administration of physiologic dosages of cortisol may be continued with suitable ulcer therapy without preventing healing of the ulcer.<sup>2,7</sup> Printed instructions, such as those on page 21, are helpful for patients to keep in a prominent place at home, such as a bulletin board or refrigerator door, where they can be referred to easily.

Patients who have been totally adrenalectomized or who have more severe degrees of adrenocortical deficiency can usually be satisfactorily maintained on cortisol in a dosage of 10 mg at breakfast and lunch, 5 mg at supper, and 10 mg at bedtime. Supplementary sodium-retaining activity may be necessary, and 9-alpha-fluorohydrocortisone (9-alpha-FF, marketed as Florinef®), 0.05 to 0.1 mg daily or three times weekly, is sufficient in most cases. Patients with spontaneous chronic adrenal deficiency may not require supplementary sodium-retaining steroid unless

they are given one of the derivatives of the natural glucocorticoids that has less sodium-retaining activity. Prednisone, prednisolone, triamcinolone, methyl-prednisolone, or dexamethasone are therefore less satisfactory in the treatment of adrenal deficiency, where all of the physiologic properties of cortisol, including sodium retention, are needed.

Cortisol is available commercially as 5,10, or 20 mg scored tablets from the Upjohn Company under the trade name of Cortef®, or as 10 or 20 mg scored tablets from Merck and Company, Inc. under the trade name of Hydrocortone®. Occasionally, a patient is encountered who is allergic to one of the ingredients used by these pharmaceutical companies in the filler for tablets of cortisone or cortisol, developing an allergic dermatitis or other mild allergic reaction whenever these tablets are taken in physiologic dosage. Pharmacologic dosages, by contrast, appear to protect against these as well as against other allergic manifestations. Because these mild allergic reactions are apparently due to sensitivity to lactose or cornstarch, both of which are used in the filler of cortisone or cortisol tablets by current manufacturers, changing to a different manufacturer's product does not usually correct the problem. Sometimes prescribing 10 mg or 20 mg tablets to be broken into halves or quarters respectively to obtain 5 mg dosages with less filler may help to avoid this problem. Otherwise, capsules containing 5 mg in a non-allergenic filler are available from a few pharmacists, but some capsules may have different absorption rates from commercial tablets and this may affect this optimum schedule of administration. A few patients have been willing to take a pediatric liquid preparation of cortisol that is too sweet for many adults. Hence, if small, subreplacement dosages become more widely used, hopefully pharmaceutical manufacturers will provide tablets with non-allergenic fillers.

Surprisingly, package inserts for cortisol still do not mention the differences between physiologic and pharmacologic dosages and effects, implying that any of the many alarming side-effects that are listed may occur with treatment at any dosage level and thus unnecessarily alarming patients who need physiologic amounts of this normal hormone in order to live normal lives! This unfortunate situation was first pointed out by Thorn in 1966 and discussed in the first edition of this book (Chapter 2, page 20) as well as in Chapter 2 (p. 18) of this edition. With the increasing potential for the use of physiologic dosages described in this book, hopefully it will be corrected soon.

In addition to supplementary sodium-retaining activity as provided

by small doses of 9-alpha-FF, women with severe adrenal insufficiency may require supplementary androgen to achieve optimum strength and sense of well-being. This is not surprising since their chief source of androgen is normally their adrenals. Unfortunately, natural adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione are not generally available for clinical use, but some pharmacists have 5 mg capsules of DHEA. Otherwise, 5 mg linguets of methyl testosterone maybe helpful to provide androgenic effects. As will be discussed later, there is evidence that DHEA is a better replacement androgen for adrenal deficiency than testosterone.

When a patient with adrenal insufficiency encounters stress, additional cortisol is necessary to maintain normal health and sense of well-being. This can vary from the extra 10 mg that may be taken by the businessman who has an unusually strenuous day ahead to the several hundred milligrams per day that may be required in the presence of an acute overwhelming infection. When a patient needs additional steroid, he or she first notices a sensation of fatigue that will disappear as soon as sufficient cortisol is taken. If supplementary glucocorticoid is not taken by patients with more severe degrees of adrenal deficiency, the fatigue may progress to malaise and generalized aching similar to that experienced when a person is developing influenza. If additional steroid is still not taken, nausea, vomiting, and collapse with a high fever, fall in blood pressure, and shock may ensue. Before cortisone and cortisol became available, this condition was not uncommon in patients with Addison's disease and was known as an "adrenal crisis." This condition is rarely seen today, and such patients should be hospitalized where they will usually respond satisfactorily to 50 mg hydrocortisone sodium succinate (Solu-Cortef®) by intravenous (IV) push, followed by 100 mg of Solu-Cortef in 1000 ml 5 percent dextrose in saline by continuous IV drip over eight hours. This should be followed by additional Solu-Cortef intramuscularly every six hours in doses dependent upon the patient's response. The intramuscular route is usually preferable except in cases of circulatory collapse because it permits more flexibility of other intravenous therapy and it also decreases the tendency to hypokalemia with its toxic effects that can result from excessive cortisol effects.

If the patient is unable to take oral nourishment, supplementary potassium should be given parenterally after the first liter of IV fluid to prevent hypokalemia. This can be satisfactorily achieved by adding 15 mEq potassium chloride to each liter of intravenous fluid after the first

until the patient is able to take oral nourishment containing potassium such as broth or orange juice. The sodium-retaining effect of these dosages of cortisol is sufficient so that supplementary sodium-retaining steroid has not been necessary. Cortisone is not advised for parenteral administration or when rapid replacement of cortisol deficiency is needed because it must be converted to cortisol before producing physiologic effects and this may require several hours.

After the patient feels well, the dosage of cortisol may usually be rapidly tapered to a maintenance level depending upon the nature of the stress causing the acute deficiency. If the dosage is not tapered sufficiently promptly, the patient may develop a transient psychosis of a "toxic" type or hypokalemia sufficient to cause arrhythmia or weakness. The latter may be mistaken for evidence of an inadequate amount of glucocorticoid, and if more is given, the patient's condition will worsen instead of improve. If this is any question, a serum potassium level or an electrocardiogram, which will show characteristic changes with hypokalemia, should be obtained. As soon as the patient feels well, therefore, it is advisable to taper the dosage of cortisol to a maintenance level as quickly as possible. This can usually be achieved by decreasing the daily dosage by 20 mg until a satisfactory maintenance level is reached.

Hence, a patient with adrenal insufficiency under stress requires dosages of cortisol to maintain a physiologic state that would produce hypercortisolism with its well-known undesirable effects in the unstressed state. That such larger dosages are maintaining a physiologic state during increased stress is evidenced by the normal blood cortisol that may be found between dosages in these patients, consistent with the statement of Ingle<sup>8</sup> that "The increased secretion of adrenal hormones serves to meet an increased need during stress and tends to maintain homeostasis rather than to disturb it. The increased secretion does not cause a state of hypercorticism such as develops when the titer of these hormones is increased artificially in the absence of need." Hence, a patient with adrenal insufficiency under stress may require dosages of cortisol to maintain a physiologic state that would produce hypercortisolism with its well-known undesirable effects in the unstressed state.

Patients with adrenal insufficiency should, therefore, be instructed to take extra cortisol when they begin to feel unusually fatigued. If they seem to be developing a respiratory infection, they should increase their daily maintenance dosage depending upon the severity of symptoms, and they should take additional steroid until a sense of well-being is

restored. For most patients doubling their maintenance dosage to 10, 15, or 20 mg four times daily is usually adequate. As soon as they feel completely well, they should return to their basic maintenance dosage. For more severe illnesses, such as acute influenza, immediately increasing the dosage of cortisol to 20 mg four times daily until they feel completely well, which usually occurs within three or four days, then decreasing to 15 mg four times daily for one day, then to 10 mg four times daily for one day, then to the basic dosage of 5, 7.5, or 10 mg four times daily thereafter, is usually adequate. In some severe illnesses, it may be necessary to increase the dosage of cortisol to as much as 120 mg daily (30 mg four times daily) in order to achieve optimum clinical improvement. Once this has been achieved, tapering the dosage by 20 mg daily until the maintenance dosage is reached has usually been satisfactory. It is also advisable for patients to contact their physician as soon as possible in order that any associated infection or other illness may be diagnosed and treated.

If their illness is associated with nausea and vomiting, as in acute gastroenteritis or "intestinal flu," cortisol should be given parenterally as soon as possible, and continued every eight hours until oral medication can be retained. Usually one intramuscular injection is adequate, but an oral dosage twice the maintenance dosage should be continued until the patient feels well. For this reason patients with adrenal insufficiency should always have vials of cortisol (Solu-Cortef®), with sterile syringes and needles for parenteral administration in their homes, and if they are traveling, in their personal luggage, and they and members of their families should be instructed in their use.

Because it is difficult and expensive to obtain medications away from home, patients should be advised to take at least two supplies of their medications, including hydrocortisone sodium succinate (Solu-Cortef, the Upjohn Company) in Mix-O-Vials with sterile syringes and needles, when they are traveling. One supply should be packed in their luggage, and one should be carried on their person. Hence, if one is lost, the other is available. This is especially important on trips outside the United States.

Patients with adrenal insufficiency should also be cautioned to carry identification cards stating their diagnosis, treatment, and the name, address, and telephone number of the physician to be notified in case of an emergency. Medic-Alert (the Medic-Alert Foundation, 1-800-432-5378) bracelets or necklaces are very good for this type of identification. Such

information might be life-saving in case of an accident in which the patient is rendered unconscious, and it is always helpful for any physician who does not know the patient's medical history. Children taking physiologic dosages of cortisol should be given notes to their teachers and school nurses stating their diagnoses and treatment and their need to take a dosage at lunchtime. If they can be maintained on an every eight hour program, this might avoid their having to take a dosage during school hours.

When patients with adrenal insufficiency are treated according to these principles, they can live perfectly normal, healthy lives. In some respects they seem to be healthier than many persons without adrenal insufficiency in that they often appear to have more energy, less fatigue, and a greater resistance to at least some types of infection. This will be discussed in greater detail later, but at this point it should be noted that when adrenally insufficient patients with common respiratory infections are treated according to these principles, no increased incidence of complications occurs, and antibiotic therapy is not necessary nor advisable unless a bacterial infection is present; otherwise, he or she may unnecessarily become resistant to that antibiotic at times of future infections.

A review of several case histories may be helpful in understanding some of the therapeutic points that have been mentioned.

### **Case 1**

The first patient with adrenal insufficiency to be treated with cortisone in our clinic was a young woman who was seen initially in 1949 at the age of twenty-nine years complaining of progressive weakness, malaise, and diarrhea of approximately six months duration. Increased pigmentation of her skin, absence of axillary hair, and low blood pressure strongly suggested adrenal insufficiency, and failure to respond to ACTH with a decrease in circulating eosinophils was consistent with that diagnosis. Present methods of measuring plasma cortisol and ACTH were not available then. There was no history of tuberculosis or evidence of this disease, so a diagnosis of Addison's disease of unknown etiology was made.

The patient was initially treated with desoxycorticosterone acetate pellets implanted subcutaneously, plus increased salt intake and frequent feedings. Later, methyl testosterone, one 5 mg linguet daily, was added with considerable improvement in her strength and energy. In 1951, when cortisone acetate became available for general clinical use, it was added to her therapy, but because she was our first patient with adrenal insufficiency to receive this medication for maintenance therapy, an optimum dosage schedule was not known.

Initially the patient was told to take a single dose of 12.5 mg daily. Later this was

increased to 12.5 mg twice daily with impressive symptomatic improvement, then to 12.5 mg every eight hours with further improvement, but she did not reach an optimum clinical state until she received a dosage of 10 mg before each meal and 5 mg at bedtime. In 1957, 9-alpha-FF was given orally in place of the subcutaneous desoxycorticosterone pellets, and a dosage of 0.05 mg three times weekly achieved adequate supplementary sodium-retaining effect while she was receiving the 35 mg of cortisone acetate.

The patient was told to double her dosage of cortisone acetate in the event of the development of an upper respiratory infection, but later it became evident that an increase in dosage to 80 mg daily (20 mg four times daily) enabled her to recover from respiratory infections more quickly, and an increase to 120 mg (30 mg four times daily) enabled her to withstand an attack of acute influenza without serious problems. The patient's previous history was interesting in that after she had had one full-term delivery, her menstrual periods had stopped several years before she developed symptoms of adrenal insufficiency. Urinary gonadotropin excretion was normal. A dosage of 1.25 mg of conjugated estrogens daily for three weeks on and one week off produced regular withdrawal menstrual flow. At age forty-five, urinary gonadotropins were elevated, so cyclic Premarin<sup>®</sup>,\* 1.25 mg daily, was continued until age fifty-six. She was last contacted at age fifty-eight, when I retired from full-time practice. At that time she was apparently healthy with normal energy and strength.

This patient demonstrated the benefit of androgen administration to women with adrenal insufficiency, with further improvement from cortisone acetate, but this had to be given in four divided doses to achieve an optimum therapeutic effect. Her clinical course also demonstrated that an increase in cortisone dosage to 80 mg daily enabled her to recover from respiratory infections with little difficulty, and an increase to 120 mg daily enabled her to withstand acute influenza without serious problems. With the now known relationship between adrenocortical and ovarian function, it is possible that her amenorrhea may have been related to her adrenal disorder, but replacement dosages of estrogen were continued up to the menopause, so there was no opportunity to observe whether normal ovarian function might have resumed with cortisone therapy in a manner similar to that of other patients (Cases 3 and 4). She further demonstrates that a patient with adrenal insufficiency can live a relatively normal life with suitable replacement therapy, since she was still quite well twenty-nine years after the condition was diagnosed.

---

\*A list of generic names for proprietary pharmaceuticals mentioned in the text appears in the Appendix, pp. 185-187.



**Case 2**

This case is an example of a combination of several hormone disorders, including primary adrenal insufficiency. The patient was a fifty-seven year old woman who, at age seventeen, had a hyperactive goiter removed surgically. About two years later, she developed malaise and easy fatigue and began having upper respiratory infections that lasted a month or more. At age twenty-two, she developed acute appendicitis; when an appendectomy was performed, she suffered postoperative collapse, but she recovered with general supportive measures.

Easy fatigue and frequent respiratory infections persisted, until at age twenty-seven a diagnosis of Addison's disease was made. No prior history of tuberculosis in the patient or in her family was known. Desoxycorticosterone acetate pellets were implanted subcutaneously. Menses were somewhat irregular. She was married at age twenty-nine, used no precautions, but had no pregnancies. In 1953, at age thirty-two, cortisone acetate therapy was started at another clinic in a dosage of 12.5 mg every twelve hours with occasional increase for malaise. She not only felt better, but had no respiratory infections for the next six or seven years. At age forty a recurrence of hyperthyroidism was treated with radioactive iodine.

At age forty-seven, shortly after she was referred to me, she had an attack of influenza with a temperature of 102°. Her cortisone dosage was increased to 12.5 mg four times daily, and she recovered uneventfully. She felt so much better during her convalescence when she was taking 7.5 mg of cortisol four times daily that this dosage was continued. She not only had more energy than she had while taking 12.5 mg twice daily, but her skin pigmentation decreased for the first time. Because hypothyroidism developed following radioactive iodine treatment, l-thyroxine (Synthroid®), 0.05 mg daily, was added.

At age forty-nine, a nodule was noted in the right breast, and at surgery, which was undertaken less than a week after the nodule was first noted, carcinoma was found in both breasts with metastatic involvement of the nodes in the left axilla. A bilateral radical mastectomy was performed, followed by postoperative radiation therapy to the axillae and chest. At the time of surgery, supplementary hydrocortisone sodium succinate was administered in a dosage of 100 mg intramuscularly one hour preoperatively and every eight hours for two doses following surgery, and subsequently gradually reduced. Because postoperative irradiation was administered, she was given 20 mg cortisol orally four times daily until this therapy was completed. She was subsequently maintained on cortisol 7.5 mg four times daily, and there was no evidence of recurrence of her cancer during the ensuing seven years. Menses tapered and stopped at age fifty-one. At age fifty-three, her blood FSH was 121 mIU/ml, blood estrogen was 28.0 pg/ml, T<sub>3</sub> sponge uptake was 45 percent, and T<sub>4</sub> was 6.4 mcg%.\* She experienced moderately severe hot flashes and some arthritic symptoms, but otherwise felt well and was living a normal life at the time I retired from full-time practice when she was age fifty-six.

\*Normal ranges for tests in Case Summaries are listed on p. 188.

This is an example of the occurrence of spontaneous Graves' disease, a known autoimmune disorder, and spontaneous adrenal insufficiency, a possible autoimmune disorder, in the same person. The history of irregular menstrual periods and infertility indicates some abnormality of the pituitary-ovarian axis, and the development of carcinoma in both breasts around the time of the menopause raises a question whether this disease might also be related in some way to her other endocrine abnormalities. In spite of these serious diagnoses, she has lived a relatively normal life for seven years following radical mastectomy. The increased incidence and severity of respiratory infections prior to treatment of her adrenal insufficiency contrasted with the increased resistance to such infections while taking cortisone acetate or cortisol. This possible relationship is discussed further in Chapter 9.

### Case 3

This case is another example of spontaneous adrenal insufficiency that demonstrates the subtle relationship that exists between function of the adrenals, ovaries, and thyroid glands. The patient was referred at the age of twenty-eight years because of amenorrhea following discontinuance of an oral contraceptive. The menarche had occurred at age thirteen, and cycles had been regular at monthly intervals, menses lasting five to six days. She had been married at age twenty and had full-term caesarean sections at ages twenty-one, twenty-two, and twenty-three years. She did not nurse any of her babies. After her third section, she required a transfusion and experienced a transfusion reaction. Subsequently she felt chronically fatigued. After one spontaneous menstrual flow, she was given an oral contraceptive cyclically for about fifteen months. When this was discontinued, spontaneous menses did not resume. Withdrawal bleeding occurred after various progestational agents. Occasional hot flashes were experienced, but she also was sensitive to cold. Her energy had continued to be poor. Salpingograms and a D. & C. had been reported normal. Her previous history had been negative except for a tonsillectomy at age six. Her mother had a total hysterectomy for an unknown cause at age thirty-four.

Physical examination was within normal limits with a height of 62 inches, weight 101½ pounds, blood pressure 95/70, and pulse 72 and regular. Urinary 17-KS were 1.5 mg/24 hours and urinary cortisol metabolites (similar to 17-OHST) were 2.3 mg/24 hours, both definitely low values. Urinary gonadotropins were within normal limits. After 80 units of ACTH gel intramuscularly, urinary 17-KS and cortisol metabolites did not change significantly, consistent with the presence of primary adrenal insufficiency. On cortisol (Cortef) 5 mg four times daily, she experienced marked symptomatic improvement and a resumption of spontaneous menses. These occurred at irregular intervals, however, so the dosage of Cortef was increased to 7.5 mg four times daily. Cycles were still irregular, so Euthroid®, gr 1 daily, was added even though thyroid tests were within normal limits: T<sub>3</sub> index = 0.91 (normal 0.8-1.2), T<sub>4</sub> 6.6 mcg% (normal 5.0-10.0). Serum cholesterol was slightly high,

however, (266 mg%, with a normal range of 150–260 mg%), and she was sensitive to cold. On this program she conceived in 1972 and had a full-term caesarean section nine months later. During her pregnancy, she took cortisol, 10 mg four times daily, and Euthroid, gr 1 daily. Her obstetrician had her discontinue the Euthroid in the eighth month.

After delivery, the patient received an injection to inhibit lactation, since she was not nursing her baby. Cortisol was resumed in a dosage of 10 mg four times daily. She returned to my office four months later without having had any spontaneous menses, and she failed to have withdrawal flow after medroxyprogesterone acetate (Provera®), 5 mg daily for five days. The dosage of cortisol was decreased to 5 mg four times daily, and she resumed spontaneous menses about a month later, but her cycles were quite irregular.

Six months later, an ACTH test revealed a baseline plasma cortisol at 10 AM of 21.5 mcg% (2½ hours after her last dose of 5 mg cortisol). An hour after an intramuscular (I.M.) injection of 25 units of ACTH, the plasma cortisol was 28.2 mcg%, consistent with persistent adrenal insufficiency.

The dosage of cortisol was increased to 10 mg before breakfast and lunch, 5 mg before supper, and 10 mg at bedtime, with improvement in energy, but the patient read newspaper and magazine articles about the dangerous effects of cortisone therapy so she kept skipping doses and trying to wean herself off the medication. Each time she did this, she developed increased fatigue and malaise, so treatment was resumed. In 1976, another ACTH test performed with an I.M. injection of 25 units of Cortrosyn again failed to demonstrate an adrenal response. Plasma follicle-stimulating hormone (FSH) at that time was normal, but T<sub>3</sub> sponge uptake was 37 percent (normal 40–60%), and T<sub>4</sub> was 3.6 mcg% (normal 4.0–10.0). Because she had no symptoms of hypothyroidism, T<sub>3</sub> by RIA was measured, and this was 155 ng/100 ml, a value well within normal limits (90–200).

She therefore not only had adrenal insufficiency, but also evidence of abnormal thyroid function characterized by a low T<sub>3</sub> sponge uptake and T<sub>4</sub> with a normal triiodothyronine level in the blood.

She failed to return for follow-up until two years later. During the previous year, she had repeated respiratory infections and had become more sensitive to cold. T<sub>3</sub> sponge uptake was 35%, T<sub>4</sub> 3.3, and T<sub>3</sub> by RIA had decreased to 20 ng/100 ml. The diagnosis of hypothyroidism was no longer in question, and Euthroid, gr 1 daily, was resumed with restoration of normal health and regular menses.

That this patient developed adrenal insufficiency after a transfusion reaction following her third caesarean section raises a question of possible etiologic relationship. Could the transfusion reaction have initiated an autoimmune process that damaged her adrenals and possibly also her thyroid gland? She later developed post-contraceptive pill amenorrhea with normal FSH, and she resumed menses and conceived when replacement cortisol and thyroid therapy were administered, subsequently having another full-term, normal pregnancy. Her obstetrician did not

maintain communication with her endocrinologist during her pregnancy and delivery, and this may have affected her postpartum course, since it is usually advisable for patients to continue physiologic dosages of cortisol and thyroid up to the time of delivery, then resume these medications postpartum in the dosages the patient was taking at the time she conceived.

The resumption of menses postpartum was apparently affected by her replacement dosage of cortisol and probably also by the cessation of thyroid medication. Post-contraceptive amenorrhea is now known to be sometimes associated with an elevated level of plasma prolactin, but a test for it was not available at that time. She had no evidence of persistent lactation, however. Although she did not resume thyroid medication postpartum, she did not develop definite clinical evidence of hypothyroidism until six years later, and her menstrual cycles did not become regular until thyroid replacement therapy was administered in addition to cortisol. She is one of numerous patients who have become alarmed by literature that emphasizes the hazards of glucocorticoid therapy without mentioning that cortisol is a natural hormone necessary for normal health and energy.

#### **Case 4**

This patient was totally adrenalectomized for Cushing's syndrome. The young woman was referred in 1967 at the age of twenty-four years with a chief complaint of rounding of her face and increased hair growth for the previous year. The menarche had occurred at age thirteen, and her cycles had always been irregular with intervals of thirty to sixty days, menses lasting five days without cramps. She had been married seven years previously and had a daughter six years old. She had had no difficulty conceiving and her pregnancy was normal. She did not nurse her baby, and menses resumed uneventfully.

Four impacted wisdom teeth had been removed at age twenty-one, and the patient thought her problems started after this dental surgery. For two years prior to her initial visit, she had been more nervous, changed from being sensitive to cold to sensitive to heat, and developed diarrhea about once weekly. During the previous year, she had noted more rounding of her face and some increased hair growth on her face. A gynecologist had performed a wedge resection of her ovaries 6 months before her visit. The ovaries were said to be only slightly enlarged, but bilateral cysts were present. Her menses continued to be irregular. Her weight had increased from 115 to 122 pounds over the previous year. Her mother and maternal grandmother had had thyroid operations, and her maternal grandmother also had diabetes mellitus. There was no family history of hypertension.

Physical examination revealed a young woman with definite rounding of the face

and moderate hirsutism of the face and periareolar areas. Height was 63 $\frac{1}{4}$  inches, weight was 122 pounds without shoes. Mild acne was present on the shoulders and back, but there were no striae. Blood pressure was 165/105, pulse 96 and regular. The thyroid was not enlarged, and there was no lymphadenopathy. Breast development was normal with slight deep induration on the right. There was no edema, and no bruises were present. The remainder of her examination was not remarkable. Plasma cortisol at 8 AM was 23.0 and at 4 PM was 31.8 mcg%. Urinary 17-KS were 19.6 and cortisol metabolites 22.5 mg/24 hours. A brisk response to ACTH stimulation occurred, and dexamethasone suppressed plasma cortisol and urinary 17-KS and cortisol metabolites to normal. An x-ray of the skull showed no enlargement of the sella turcica. A diagnosis of Cushing's syndrome with adrenal hyperplasia was therefore made.

She was given sufficient dexamethasone to keep her steroid levels normal, but her adrenals continued to become hyperactive whenever the dosage of dexamethasone was decreased, and cushingoid features worsened while she was taking this medication. A total bilateral adrenalectomy was therefore performed at age 25. Postoperatively she was maintained on cortisol, 10 mg four times daily, and a 9- $\alpha$ -FF, 0.1 mg three times weekly. After surgery, her blood pressure became normal but gradually increased from 130/85 to 140/100, so the 9- $\alpha$ -FF was tapered and discontinued. Hydrodiuril®, 50 mg daily, and later Inderal®, 10 mg four times daily, caused the blood pressure to decrease to 125/90. After approximately a year, the hydrochlorothiazide was discontinued without significantly affecting the blood pressure, and later Inderal was discontinued. For the next three years, her blood pressure varied between 120 and 140/80 to 100 with no antihypertensive medication.

In spite of her maintenance therapy, the patient continued to complain of chronic fatigue, so a month after adrenalectomy dehydroepiandrosterone (DHEA), 5 mg by mouth twice daily, was started. A limited supply of this steroid had been provided by Ayerst Laboratories for clinical investigation. This produced impressive improvement in her energy, and she developed spontaneous menses at monthly intervals, the first time she had ever had regular menstrual cycles. Because our supply of DHEA was limited, it was discontinued after she had achieved optimum clinical improvement on four different occasions. Each time the steroid was stopped, fatigue and irregular menses returned, sometimes associated with functional bleeding, and she also noted that she bruised more easily when she was not taking this steroid.

When it was resumed, energy improved, menstrual cycles became regular, and she no longer bruised easily. Other androgens, including methyl testosterone, Halotestin®, and testosterone propionate were tried, but none of these restored normal menses or produced as much improvement in energy as the DHEA. Vitamin C, 100 mg daily, was also tried, but it did not produce the clinical improvement noted with DHEA.

Follow-up skull x-rays were normal. At age 30, five years after adrenalectomy, her pigmentation, which had increased initially, appeared to be definitely subsiding.

Urinary FSH was 10 mouse uterine units (m.u.u.) and total estrogens 29  $\mu\text{g}/24$  hours, both within normal limits for a female. She was not taking DHEA at the time of these tests. Six years postadrenalectomy plasma ACTH by RIA was 49.9 pg/ml (normal 15-100). The following year, at age 42, her medication was changed from cortisol to cortisone acetate, 10 mg before breakfast, lunch and at bedtime, and 5 mg before supper, and she thought this caused less tendency to indigestion.

In October, 1975, our supply of DHEA again was exhausted, and shortly after that her menses ceased and she noted increased fatigue. Later, methyl testosterone, one 5 mg linguet daily, or Halotestin, 2 mg daily, seemed to restore strength and menses, but not as well as DHEA. Two years later (nine years post-adrenalectomy), plasma DHEA-S (dehydroepiandrosterone sulfate) was 13 mcg/dl (normal 80-390 mcg/dl). A new supply of DHEA, 5 mg daily, helped restore energy and regular, normal menses. Emotional problems related to various stresses incurred in raising a family developed, but slight changes in dosages of cortisone and thyroid seemed to help, and she was eventually stabilized on cortisone acetate 15-15-10-10, DHEA 5 mg daily, and Euthroid, gr. 1 before breakfast and gr  $\frac{1}{2}$  before supper daily.

Nineteen years post adrenalectomy, at age 44, our supply of DHEA was again exhausted, but Halotestin, 2 mg daily, seemed to help almost as well, with a continuation of regular menses and adequate energy and strength. She is now age 51 and living an apparently normal life on her replacement therapy of cortisone acetate, 15-15-10-10, Halotestin, 2 mg daily, and Euthroid-1, twice daily.

This patient has been followed for twenty-six years after a total bilateral adrenalectomy for Cushing's syndrome. Although she has lived a reasonably normal life, evidence was impressive that supplementation with DHEA provided better replacement than other commercially available androgens. Andrews<sup>9</sup> has reviewed the experimental evidence for possible mechanisms of reproductive suppression by increased ACTH secretion, but it also appears that a deficient production of DHEA may have a similar effect.

DHEA is a normal hormone that is apparently produced in larger quantities under unstressed circumstances than any other adrenocortical hormone, yet very little is known about its contribution to normal health, presumably due to its failure to be protected by a patent. It is a relatively weak androgen, but it is a precursor of both estrogen and testosterone, and observations such as those made on this patient indicate that its deficiency can interfere with normal ovarian function. While pharmaceutical companies are investing millions into the development of new medications, it is surprising that no attempt has been made to determine the potential value of this normal hormone that has been known for over 40 years to the maintenance of optimum health.

## MILD ADRENOCORTICAL DEFICIENCY

As mentioned previously, mild adrenocortical deficiency, either primary (low adrenal reserve) or secondary to inadequate stimulation by the pituitary or the hypothalamus, is another clinical disorder in which physiologic dosages of cortisol have a rational role in therapy. Low adrenal reserve is characterized by a subnormal response to ACTH with baseline plasma cortisol level within normal range. Because of their residual adrenocortical function, patients with this disorder can sometimes omit the bedtime dose of cortisol. Mild secondary adrenocortical deficiency is characterized by a baseline plasma cortisol level either low or in the low normal range, but with a normal response to Cortrosyn stimulation.

An impressive number of patients with unexplained chronic fatigue have been found to have mild adrenocortical deficiency, either primary or secondary, and the administration of cortisol in a dosage of 5 mg four times daily has resulted in clinical improvement that is often dramatic. Many of these patients have been studied intensively prior to being referred for endocrine evaluation, receiving various other types of therapy, including vitamins, iron, and thyroid medication, without benefit. That many had been told their fatigue must have a psychogenic basis when previous studies had failed to demonstrate any evidence of organic disorder emphasizes the importance of this condition.

Patients with psychiatric disorders, especially anxiety and depression, frequently complain of chronic fatigue, but their baseline plasma cortisols tend to be high and their adrenals characteristically are hyperresponsive to ACTH,<sup>10,11</sup> so a Cortrosyn test should distinguish them from patients with mild adrenal deficiency. Patients with mild adrenal deficiency describe wanting to do things but feeling too exhausted to undertake them, and they usually present no evidence of serious psychologic problems. Their fatigue is usually present throughout the day, often being noted when they first awaken in the morning, whereas the fatigue complained of by hypothyroid patients often does not develop until afternoon or evening. Patients with known psychologic problems who complain of fatigue should also have Cortrosyn tests, because in some cases it appears that the chronic fatigue resulting from mild adrenal deficiency has aggravated a psychic disorder, and if the chronic fatigue can be helped, the psychologic disorder may also be benefited. Other conditions that often are associated with mild adrenocortical deficiency

are functional hypoglycemia (Chapter 10), allergic disorders (Chapter 7), and autoimmune disorders (Chapters 6 and 8).

The etiology of mild adrenal deficiency is not known, but it is interesting to note that heavy cigarette smoking<sup>12</sup> and ingestion of moderate amounts of coffee<sup>13</sup> have been found to cause significant rises in plasma and urinary 11-hydroxycorticosteroid concentrations, possibly due to enhanced ACTH release resulting from nicotine—or caffeine—induced increase in sympathetic and catecholamine activity. Whether prolonged adrenocortical stimulation from these or other causes could result in mild adrenal deficiency in susceptible persons remains speculative.

The possibility that ascorbic acid deficiency might cause low adrenal reserve should also be studied. The highest concentration of ascorbic acid in the body occurs in the adrenal cortex, but its function there has never been elucidated. Presumably it plays a role in the production of adrenocortical steroids. Administration of large dosages of vitamin C has been reported to have a protective effect against the common cold as well as some other beneficial effects that have been noted with physiologic dosages of cortisone or cortisol,<sup>14</sup> so a relationship would not be surprising.

It should be emphasized that clinical improvement from physiologic dosages of cortisol may not become evident for up to two weeks after the initiation of this therapeutic program, so patients should be cautioned not to become discouraged if they do not feel better immediately.

Even though plasma cortisol and ACTH levels and response to Cortrosyn stimulation tests may be within normal range, patients with unexplained chronic fatigue may still warrant therapeutic trials with a small dosage of cortisol since the interference with normal daily living described by these patients is sufficient to warrant careful investigation, and since the chances of restoring energy and a sense of well-being seem to be quite good.

Several case histories provide examples of the value of this type of therapy in patients with low adrenal reserve.

### **Case 5**

The patient was a fifty-six year old female who had experienced episodes of nausea and fainting for approximately twenty years. At first, these episodes would occur at intervals of one or two years, but at about age fifty-four they became more frequent, as often as once a week. They were usually associated with headache. At age fifty-four, she was admitted to a hospital where a neurological consultation reported no evidence of abnormality, but blood sugar was noted to be low three



hours after glucose administration during a routine glucose tolerance test. X-rays of the skull, and brain and liver scans were all normal, and she was discharged with a diagnosis of functional hypoglycemia.

After discharge, she experienced little benefit from dietary therapy and began to complain of chronic fatigue as well, so at age fifty-six she was referred for an endocrinologic evaluation. Because she was receiving medications including Dilantin®, Bellergal®, and Pro-Banthine®, some of which might interfere with plasma cortisol determinations, and because her symptoms were somewhat suggestive of adrenal insufficiency, she was given a therapeutic trial with cortisol, 5 mg four times daily.

She returned two weeks later reporting dramatic improvement. She was, therefore, tapered off of all medications. A week after discontinuing cortisol, her plasma cortisol at 9 AM was 19.3 mcg%, and one hour after an I.M. injection of 25 units of ACTH this rose to 38.2 mcg%, an apparently normal response. She developed weakness and fatigue off the medication, however, so cortisol was resumed in a dosage of 5 mg four times daily, with another impressive subjective response.

It was therefore decided to obtain a metopirone test to check on the possibility of hypopituitarism causing her symptoms, but this test also was within normal limits. Cortisol had been discontinued the day before the metopirone test was started. She was then instructed to discontinue the cortisol for six weeks, following which a second ACTH test showed very clear evidence of low adrenal reserve, with a baseline plasma cortisol level of 21.7 mcg% at 9 AM and a rise to only 26.7 mcg% after ACTH. Meanwhile, she had again developed symptoms of frequent headaches, nausea, chronic fatigue, and malaise. She again improved after the resumption of cortisol, 5 mg four times daily.

The patient still tired somewhat easily, however, and when she developed an upper respiratory infection and her dosage was increased to 10 mg four times daily, she stated she felt so much better that her maintenance dosage was increased to 7.5 mg four times daily. She has continued to feel quite well on this dosage. At the time of this report she had received this therapy for a total of five years, during which time she had no undesirable side effects and felt better than she had for many years. She experienced several respiratory infections, but when her dosage was doubled, she recovered promptly. On two occasions, she was given penicillin and on two occasions erythromycin for sinusitis during this period.

This case demonstrates how unexplained nausea and faintness, especially when associated with functional hypoglycemia, should suggest the possibility of adrenal insufficiency. It also demonstrates how therapy with glucocorticoid can result in a temporary restoration of adrenal reserve that may relapse after glucocorticoid is withheld for several weeks. In addition, she provides an example of how respiratory infections can be well tolerated with the therapeutic glucocorticoid program recommended.

## Case 6

This patient was a fifty-one year old female. She had reached the menarche at age fourteen with regular cycles at intervals of twenty-eight days until she went to college, when menses ceased. They resumed at the time of spring and summer vacations, however, consistent with a diagnosis of "psychogenic amenorrhea." She was married at age twenty-two, used no precautions, but was unable to conceive. Her husband was found to have a low sperm count, so they adopted two children.

At age forty, the patient had operations for bilateral inguinal hernias, and the surgeon noted the presence of endometriosis, so a few months later a hysterectomy and bilateral salpingo-oophorectomy were performed. She was given Premarin, 0.625 mg daily on a cyclic schedule, but hot flashes persisted, so the dosage was increased to 1.25 mg cyclically. This corrected the hot flashes, but she developed intermittent stiffness and aching in the knees and other joints, and she tended to tire more easily.

For several years the patient had noted numbness in her hands and toes after exposure to cold and after sleeping, and this became worse. Her skin tended to be dry, and she had mild constipation.  $T_3$  sponge uptake and serum thyroxine were normal, but an ACTH test revealed low adrenal reserve with a baseline plasma cortisol of 19.4 mcg% at 9 AM and a rise to 25.9 mcg% thirty minutes after an I.M. injection of Cortrosyn. Cortisol, 5 mg four times daily, was started, and within two weeks she noted marked subjective improvement with normal energy, disappearance of arthralgias, and a general increase in sense of well-being. Cyclic Premarin therapy was maintained.

The patient continued to feel well over the subsequent five years and she also reported increased resistance to respiratory infections. Whenever symptoms of incipient respiratory infections developed, the dosage of cortisol was doubled until the symptoms cleared. On several occasions, symptoms disappeared within twenty-four hours with such therapy, suggesting that the illness had been aborted. During this time her husband had numerous respiratory infections, so there had been no apparent change in her exposure to such infections.

This patient's low adrenal reserve was initially manifested by intermittent arthritic symptoms as well as chronic fatigue following a surgical menopause. This condition has been termed "menopausal arthritis," and this patient's experience indicates the advisability of testing adrenal responsiveness in such patients. Improvement with small physiologic dosages of cortisol may be dramatic. It is tempting to speculate that the "psychogenic amenorrhea" was a manifestation of the increased stress of attending college interfering with normal pituitary-ovarian function, a disorder that may be corrected by the administration of small dosages of cortisol. Later, after bilateral herniorrhaphy and bilateral salpingo-oophorectomy, the increased demand upon the adrenals may have resulted in symptoms of fatigue and arthritis that were corrected by cortisol

administration. Cyclic Premarin therapy was continued because she had not yet reached the usual age of spontaneous menopause. She had no further symptoms of endometriosis. She is one of numerous patients who have reported evidence of increased resistance to respiratory infections while taking small doses of cortisol, and this will be discussed in more detail in Chapter 9.

Another example of low adrenal reserve is presented in case number 7.

### **Case 7**

A fifty-nine year old female had been experiencing episodes of fatigue since the age of forty-six. Her menstrual history had been normal until age thirty-five, when she developed prolonged uterine bleeding. Radium therapy to the endometrium had been administered for this, and she developed subsequent amenorrhea and hot flashes. The episodes of fatigue began about ten years later. Her previous physician had given her dexamethasone for four days empirically with suggestive benefit. Later, when her symptoms returned, she had been given various other medications, including estrogen and androgens, without apparent effect. She had also been given thyroid medication without benefit. Four months prior to her referral, she had been given prednisone, 5 mg twice daily with dramatic improvement, but when the dosage was reduced to 5 mg daily, fatigue returned. She was therefore referred as a possible case of adrenal insufficiency.

Because the patient had been taking prednisone, an ACTH test was not performed initially, but her medication was changed to cortisol in decreasing dosages. It was found that she felt best on a dosage of 7.5 mg four times daily. While receiving that dosage, she had an ACTH test that demonstrated a plasma cortisol at 10 AM of 13.7 mcg%; one hour after an I.M. injection of 25 units of ACTH this rose to 22.9 mcg%, consistent with a sluggish adrenal response. She has subsequently felt quite well on 7.5 mg four times daily. On several occasions when the dosage was decreased to 5 mg four times daily, fatigue returned, and various aches developed, especially in her shoulders and neck.

In 1975, a return of chronic fatigue occurred while the patient was taking cortisol, 7.5 mg four times daily, and it was found that she had an infected tooth. Energy returned after the dental infection was treated. She gave a history of having never had upper respiratory infections or influenza during her lifetime, nor did she have any incidence of these infections while she was taking cortisol. She had two episodes of urinary tract infection, but these responded promptly to cephalosporin therapy. Later, she had an uneventful vaginal repair of a rectocele and enterocele with a perineorrhaphy, receiving additional cortisol prior to and following her surgery. An ACTH test performed during her hospitalization showed persistent low adrenal reserve.

This is another patient who had developed symptoms of fatigue in her mid-forties, which ultimately proved to be due to low adrenal reserve. She had experienced menopause following pelvic irradiation ten years

previously. She also noted various aches and arthritic symptoms associated with chronic fatigue, and all of these symptoms were corrected by suitable physiologic dosages of cortisol. Later, the return of symptoms while she was taking cortisol was found to be due to the development of a dental infection, emphasizing the importance of looking for obscure infections in patients who have a relapse of symptoms while taking a dosage of steroid that has previously been sufficient to control their condition. This patient is also one of several patients whom we have encountered who give a history of never having had respiratory infections or influenza, suggesting the presence of an immune mechanism that provides greater than usual resistance to this type of illness. Her case is another example of how patients with adrenal insufficiency or low reserve can tolerate elective surgery uneventfully provided they are given additional cortisol prior to and following the stress.

### **CONGENITAL ADRENAL HYPERPLASIA**

Another disorder in which treatment with physiologic dosages of cortisone or cortisol is obviously indicated is congenital adrenal hyperplasia. This condition results from a relative deficiency of one of the enzymes in the pathway of production of cortisol in the adrenals. The deficiency in cortisol production leads to increased ACTH stimulation that in turn causes an excessive production of those steroids that do not require the deficient enzyme. The most common defect is in 21-hydroxylase, the enzyme that converts 17-alpha-hydroxyprogesterone to cortexolone. This deficiency is usually relative rather than absolute so that the adrenals produce an excess of androgen and other steroids that do not require this enzyme in order to supply sufficient cortisol. The clinical picture is most obvious in young girls who, as a result of androgen excess, have abnormal development of the genitalia with enlargement of the clitoris, rapid skeletal growth in early childhood but premature closure of the epiphyses, resulting in ultimate short stature, androgenic build, acne, hirsutism, and poor secondary sexual development with amenorrhea and hypoplasia of the breasts.

Treatment of the disorder consists of the administration of sufficient cortisone acetate or cortisol to reduce the excessive levels of androgen and ACTH to normal. The maximum maintenance level for the unstressed patient should therefore be 35-40 mg daily of either cortisone acetate or cortisol, and many patients can be maintained on smaller dosages.

Earlier reports suggested that larger doses might be necessary, but this was probably due to a suboptimum dosage schedule. Although these patients usually tolerate stress without developing adrenal insufficiency, they should be instructed to increase the dosages with stress in a manner similar to patients with adrenal insufficiency so as to avoid an excessive production of androgen during the stress.

With suitable therapy, patients with congenital adrenal hyperplasia will develop normally and be able to bear children provided treatment is instituted early and taken regularly in an optimum dosage. Even when treatment is started later in life, improvement is usually impressive, but fertility is less predictable. The schedule of dividing the daily dosage into four equal doses to be taken with meals and at bedtime provides a more effective suppression of excessive androgen production than a schedule of only two doses daily (Fig. 4).<sup>15</sup>

D.L. 37 YR. FEMALE, AMENORRHEA FOR 4 YRS, MODERATE OBESITY & HIRSUTISM.

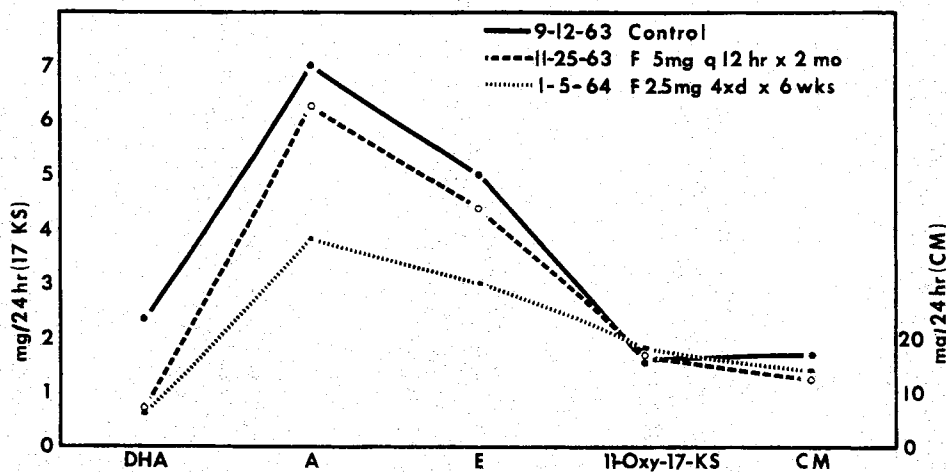


Figure 4. Effects of the same total daily dosage of cortisol administered in 2 divided doses and in 4 divided doses. F = cortisol, DHA = dehydroepiandrosterone, A = androsterone, E = etiocholanolone, 11-oxy-17-KS = 11-oxygenated 17 ketosteroids, and CM = cortisol metabolites. The values for fractions from each separate 24-hour urine collection are connected by lines to facilitate comparison. From William McK Jefferies, *Glucocorticoids and Ovulation*, in RB Greenblatt (Ed.), *Ovulation*. Copyright 1966, J.B. Lippincott Co., Philadelphia. Reprinted by permission.

Because 21-hydroxylase is also necessary for the production of sodium-retaining steroids, there is no excess of these steroids in 21-hydroxylase deficiency. In a less common type of congenital adrenal hyperplasia due

to a relative deficiency of 11-beta-hydroxylase, an excess of the sodium-retaining steroid 11-desoxycorticosterone as well as of androgens occurs, and the patients have hypertension associated with androgenicity. The pathologic physiology is still essentially the same—the adrenals are being stimulated to work overtime to produce a sufficient supply of cortisol, and in the process they produce an excess of other steroids. Hence, the treatment is the same: administration of sufficient cortisol to restore normal levels of the other steroids. In patients with 11-beta-hydroxylase deficiency, treatment with cortisol not only counteracts the androgenicity but also restores blood pressure to normal, provided permanent damage to the kidneys has not occurred. These patients have an interesting combination of relative adrenal insufficiency with hypertension and emphasize that a low blood pressure is not essential for the diagnosis of relative adrenal insufficiency.

A patient who demonstrates the subtle aspects of diagnosing this type of congenital adrenal hyperplasia is described in Case 8.

### **Case 8**

This forty-three year old male was referred because of recurrent hyperthyroidism. He had had high blood pressure as long as he could remember, but he did not know what treatment he had been given for this. He had not been taking any medication for several months prior to his visit. He said he was a large baby at birth and that he had been very strong as a child. He remembered eating heartily when he was three years old, and he was unusually strong until age eighteen, when his strength seemed to leave him suddenly, about the time he had a tumor removed from his right breast. Symptoms of hyperthyroidism had developed at age thirty-seven; he took medication for this for two years with improvement.

A year before his referral, at age forty-two, he had a return of nervousness that he attributed to a vasectomy that had been performed four months previously. Six months later, he had influenza and was quite ill with complicating pneumonia. Subsequently, his symptoms of excessive nervousness and fatigue became worse. He had felt warm and had noted an increased pulse rate, but there had been no change in weight. Prior to the influenza attack, he said he had had no respiratory infection for at least ten years.

The patient denied having ever had any headaches, but his energy had frequently been poor. He was married and had three children. There was no family history of diabetes mellitus, but his mother had high blood pressure.

Physical examination revealed a height of 65½ inches, weight 152½ pounds, blood pressure 160–170/90–100, pulse 88 and regular. He was very tense and restless, with moderate hirsutism. There were no eye signs of hyperthyroidism and he had minimal tremor. The thyroid was soft, difficult to outline, approximately two-and-one-half times normal size. There was no lymphadenopathy. The remain-

der of his examination was not remarkable. White blood count was 5,900 with 76% neutrophils, 22% lymphs, 1% monocytes, and 1% eosinophils. Twenty-four hour  $I^{131}$  uptake over the thyroid was 29%;  $T^3$  sponge uptake was 67% (normal 40–60%), and  $T^4$  was 9.4 mcg% (normal 4.0–10.0).  $T^3$  by RIA was 180 mcg% (normal 65–215). Plasma cortisol at 1:15 PM was 10.9  $\mu\text{g}\%$ , a relatively low value for this time of day, but thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 27.9  $\mu\text{g}\%$ , consistent with normal adrenal responsiveness.

Because his history suggested the presence of excessive androgen at an early age plus asymptomatic hypertension for many years, a blood sample was drawn for plasma desoxycorticosterone (DOC). This was reported to be 355 ng%, with a normal range of 5–15. Repeat determinations obtained several weeks later were 275 and 349 ng%.

This patient therefore had not only symptoms suggestive of a mild recurrence of hyperthyroidism without laboratory confirmation but also congenital adrenal hyperplasia characterized by excessive production of androgen and DOC. A diagnosis of congenital adrenal hyperplasia associated with a deficiency of 11-beta-hydroxylase was therefore made. Cortisol, 5 mg four times daily, was prescribed, and his strength and sense of well-being improved impressively, but symptoms of hyperthyroidism became more pronounced;  $T^4$  increased to 12.5 mcg% and  $T^3$  by RIA to 250 ng/100 ml, so propylthiouracil, 50 mg four times daily, was added to his therapy.  $T^3$  and  $T^4$  and symptoms of hyperthyroidism returned to normal, but plasma DOC remained elevated until the dosage of cortisol was increased to 7.5 mg four times daily. Five months later,  $T^3$  by RIA was 160 ng/100 ml,  $T^4$  9.0 mcg%, and plasma DOC 6.8 ng/100 ml. Blood pressure decreased to 120–135/80–90. It was therefore evident that he not only experienced symptomatic improvement on cortisol therapy but blood pressure also decreased to normal range. Propylthiouracil was discontinued after a year, and hyperthyroidism has remained in remission.

The recurrence of hyperthyroidism with a diffuse thyroid enlargement in this patient with congenital adrenal hyperplasia, and the apparent aggravation of symptoms and laboratory evidence of hyperthyroidism after the patient received cortisol, raise a question of the possible significance of adrenocortical function in patients developing hyperthyroidism. That Graves' disease, or hyperthyroidism due to diffuse goiter, has been demonstrated to be a manifestation of an autoimmune phenomenon associated with the production of an abnormal thyroid stimulator, and the apparent relationship between autoimmune phenomena and adrenocortical function, provide support for such speculation. In addition, evidence that physiologic dosages of cortisol may increase  $T_3$  receptor function, as discussed in Chapter 10, further suggests a possible mechanism of the influence of cortisol upon thyroid function.

A deficiency of 11-beta-hydroxylase is thought to be a relatively rare cause of hypertension, but it should be considered in women with

hypertension plus associated androgenic changes or elevated urinary 17-KS and in hypertensive men, especially in younger age groups. Perhaps it may be more common than is presently suspected. It is interesting to note that an earlier report<sup>16</sup> mentioned a blood pressure lowering effect of cortisone as well as a blood pressure elevating effect of ACTH in some hypertensives. The occurrence of partial 11- and 21-hydroxylase deficiencies in patients who develop hypertension, hirsutism, and menstrual disorders in late childhood or early adulthood<sup>17,18,19</sup> has been demonstrated and termed "acquired" adrenal hyperplasia, emphasizing the importance of careful studies in such cases. An interesting feature of hypertension associated with 11-beta-hydroxylase deficiency is that it may persist for years without complications such as renal damage. The ability to test for elevated levels of desoxycorticosterone in blood or urine should simplify the diagnosis of this curable form of hypertension.

## REFERENCES

1. Orth DN, Kovacs WJ, DeBold CR: The Adrenal Cortex. In Williams RH (Ed.): *Williams Textbook of Endocrinology, 8th ed.* Philadelphia, Saunders, 1992, pp. 525-529.
2. Jefferies WMcK: Low dosage glucocorticoid therapy. *Arch Intern Med* 119:265-278, 1967.
3. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adwi F, Lahav M: Adrenocorticotropin stimulation test: Effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 72:773-778, 1991.
4. Orth DN, Kovacs WJ, DeBold CR: The Adrenal Cortex. In *Williams Textbook of Endocrinology, 8th ed.* Philadelphia, Saunders, 1992, pp. 532-533.
5. Jefferies WMcK, Kelly LW, Jr, Sydnor KL, Levy RP, Cooper G: Metabolic effects of a single intravenous infusion of hydrocortisone related to plasma levels in a normal versus an adrenally insufficient subject. *J Clin Endocrinol Metab* 17:186-200, 1957.
6. Thorner MO, Vance ML, Horvath E, Kalman K: The Anterior Pituitary. In *Williams Textbook of Endocrinology, 8th ed.* Philadelphia, Saunders, 1992, p. 286.
7. Zetzel L: The use of ACTH and adrenocorticosteroids in diseases of the digestive system. *N Engl J Med* 257:1170-1180, 1957.
8. Ingle DJ: Some further studies of the relationship of adrenocortical hormones to experimental diabetes. *Diabetes* 1:345-350, 1952.
9. Andrews RV: Influence of the adrenal gland on gonadal function. In Thomas JA, Singhal RL (Eds.): *Advances in Sex Hormone Research, Vol. 3: Regulatory*



- Mechanisms Affecting Gonadal Hormone Action*, Baltimore, Univ Park, 1976, pp. 197-215.
10. Altschule MD, Promisel E, Parkhurst BH, Grunebaum H: Effects of ACTH in patients with mental disease. *Arch Neurol Psychiatry* 64:641-649, 1950.
  11. Elithorn A, Bridges PK, Hodges JR, Jones MT: Adrenocortical responsiveness during courses of electro-convulsive therapy. *Br J Psychiatry* 115:575-580, 1969.
  12. Kershbaum A, Pappajohn DJ, Bellet S, Hirabayashi M, Shafiiha A: Effect of smoking and nicotine on adrenocortical secretion. *JAMA* 203:275-278, 1968.
  13. Bellet S, Kostis J, Roman L, DeCastro O: Effect of coffee ingestion on adrenocortical secretion in young men and dogs. *Metabolism* 18:1007-1012, 1969.
  14. Pauling L: *Vitamin C, the Common Cold and Flu*. San Francisco, Freeman, 1976.
  15. Jefferies WMcK: Glucocorticoids and ovulation. In Greenblatt RB (Ed.): *Ovulation*. Philadelphia, Lippincott, 1966, pp. 62-74.
  16. Perera GA: In Mote JR (Ed.): *Proceedings of the First Clinical ACTH Conference*. Philadelphia, Blakiston, 1950, p. 284.
  17. Gabrilove JL, Sharma DC, Dorfman RJ: Adrenocortical 11 $\beta$ -hydroxylase deficiency and virilism first manifest in the adult woman. *N Engl J Med* 272:1189-1194, 1965.
  18. Newmark S, Dluhy RG, Williams GH, Pochi P, Rose LI: Partial 11- and 21-hydroxylase deficiencies in hirsute women. *Am J Obstet Gynecol* 127:594-598, 1977.
  19. Tan SY, Noth RH, Mulrow PJ: Deoxycorticosterone and 17-ketosteroids: Elevated levels in hypertensive patients. *JAMA* 240:123-126, 1978.

## Chapter 5

### GONADAL DYSFUNCTION AND INFERTILITY

The beneficial effects of physiologic dosages of cortisone acetate and cortisol in patients with congenital adrenal hyperplasia led to their being tried in women with ovarian dysfunction, hirsutism, and acne, since this combination of abnormalities occurred in both types of conditions. The dosages of glucocorticoids initially administered were relatively large, in the range of the full replacement dosages employed in congenital adrenal hyperplasia. Improvement occurred, but the possibility of adrenocortical suppression and impairment of resistance to stress from such doses was disturbing, so progressively smaller doses were tried, and we were pleased to find that impressive improvement occurred from physiologic dosages of 5 mg four times daily or even 2.5 mg four times daily, provided treatment was continued for a sufficient length of time.<sup>1</sup> It was therefore postulated that such cases might represent variants of the adrenogenital syndrome, viz., mild disorders of adrenal steroid metabolism characterized by excessive production of adrenal androgen and estrogen in sufficient quantities to interfere with ovarian function.

At that time, assessment of adrenal steroid production was limited clinically to measurements of urinary excretion of 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OHST), resulting in indirect estimates at best, since levels of urinary metabolites might be affected by steroid metabolism in the liver and peripheral tissues, by blood levels of steroid-binding proteins, or by renal function, as well as by changes in rate or pattern of steroid production by the adrenals.

Responses of urinary excretion of 17-KS and 17-OHST of these patients to a standard stimulus with ACTH were usually consistent with normal adrenal responsiveness, but when urinary 17-KS were fractionated, excretion of dehydroepiandrosterone (DHEA), androsterone (A), and etiocholanolone (E) frequently showed much greater variation than that of women with regular ovulatory cycles.<sup>2</sup>

Later, when plasma levels of cortisol, testosterone, DHEA-sulfate,

estrogen, and FSH could be measured, it was found that some women with gonadal dysfunction that could be corrected by subreplacement dosages of cortisone acetate or cortisol had poor responsiveness to ACTH indicative of low adrenal reserve, some had elevated levels of free (or unbound) testosterone or of DHEA-sulfate, and some had elevated or low levels of estrogen and low or normal levels of FSH. Those with elevated plasma free testosterone had associated acne and hirsutism, but urinary 17-KS excretion might be within normal limits. On the other hand, some women with acne and/or hirsutism might have normal plasma testosterone with elevated urinary 17-ketosteroids, indicating the production of an excess of androgen other than testosterone, usually DHEA. Women with elevated levels of estrogen usually had metrorrhagia.

After subreplacement dosages of glucocorticoids were found to correct ovarian dysfunction in this type of patient, studies were undertaken to determine the effects of small doses of cortisone acetate on fluid and electrolyte excretion as well as urinary steroid levels.<sup>3</sup> It was found that small changes in urinary sodium and potassium excretion did occur but that these changes were corrected within eight days even though the steroid was continued (see Fig. 2). It was also noted that a new, stable level of urinary steroid excretion did not occur until approximately ten to fourteen days after these small doses were initiated. It was further found that these small doses did not interfere with the adrenals' ability to respond to a standard dose of ACTH<sup>3</sup> (Fig. 5).

The concept of a close functional relationship between the ovaries and the adrenals is not new. The steroid-forming tissues of the gonads and adrenal cortices have a common embryonic origin, and these glands share many enzymatic steps in the production of their steroid hormones. The changes in adrenocortical activity that occur at puberty and the menopause further suggest a close association between these two pairs of glands. The well-known effects of stress upon the function of both of these pairs of glands could be due to simultaneous independent effects or to a sequential effect wherein the effect of stress upon one pair of glands, e.g., the adrenals, in turn affected the function of the other pair of glands. Clinical observations that patients with disorders of adrenocortical function, such as adrenal insufficiency (Addison's disease), hyperfunction (Cushing's syndrome), or dysfunction (congenital adrenal hyperplasia), had associated disorders of gonadal function were consistent with the concept of a close relationship between these glands.

## Chapter 6

### PHYSIOLOGIC DOSAGES IN RHEUMATOID ARTHRITIS: A RELATIONSHIP TO AUTOIMMUNITY AND TO MILD ADRENOCORTICAL DEFICIENCY

The antiarthritic effects of large doses of glucocorticoids are well-known. As has been mentioned previously, arthritis was the first pathologic disorder other than adrenal insufficiency for which glucocorticoid therapy was administered clinically, and because of the type of preparation and schedule of administration, the early dosages were much larger than what was later found to be a physiologic replacement dosage. When undesirable and hazardous side effects were encountered with such large dosages, it was assumed that any dosage would be dangerous. There has, therefore, been a tendency to avoid glucocorticoid therapy in arthritic conditions except as a last resort and then to discontinue it as soon as possible.

The evidence that cortisone acetate or cortisol can be administered in safe dosages that may be taken indefinitely without harmful side effects by patients with ovarian dysfunction raised the question of whether such safe dosages might have a place in the treatment of rheumatoid arthritis. An interesting report of one of the early patients with rheumatoid arthritis treated with cortisone acetate<sup>1</sup> implies that after initial dosages of 50 mg intramuscularly twice daily he was satisfactorily maintained on oral dosages of 50 mg and later 35 mg per day. The schedule of administration was not mentioned.

Twenty-eight years ago, I reported the beneficial effects of *physiologic* dosages of cortisone acetate or cortisol on two patients with rheumatoid arthritis, with evidence that patients with rheumatoid arthritis seemed to have lower excretion of dehydroepiandrosterone in their urine and, hence, might have a mild abnormality of steroid metabolism.<sup>2</sup>

A review of the literature fails to reveal any attempts by others to confirm these observations or even any comment on them. The benefit

## Chapter 7

### ALLERGIC DISORDERS

The effectiveness of large doses of glucocorticoids in the treatment of bronchial asthma and other acute allergic phenomena is well known, but the dosages employed are sufficient to cause hypercortisolism with its undesirable and hazardous side effects if they are continued as maintenance therapy. The use of prolonged glucocorticoid therapy in chronic allergies has, therefore, been discouraged.

With the knowledge that physiologic dosages of cortisone acetate or cortisol may be continued indefinitely without harmful side effects, plus that a number of patients who were given physiologic dosages for other reasons have reported impressive symptomatic improvement in their allergic conditions, it would be advisable to determine whether administration of physiologic dosages for prolonged periods might be helpful in any chronic allergic disorder.

The rationale for this type of therapy is supported by the observation, mentioned in Chapter 4 in the discussion of low adrenal reserve, that many patients with allergies have abnormal ACTH tests, with evidence either of low adrenal reserve or of a low baseline plasma cortisol level. This suggests that allergies may be associated with an abnormality of adrenocortical function in the cases with low adrenal reserve, or of hypothalamic or pituitary function or of glucocorticoid transport in those with low baseline plasma cortisol levels.

A number of animal studies also support the rationale for this type of therapy in allergic rhinitis, allergic asthma, anaphylaxis, and some urticarias, the so-called "immediate-type" hypersensitivity disorders or Type I reactions of Coombs and Gell.<sup>1</sup> This type of allergy is characterized by increased levels of histamine in affected tissues, and administration of histamine can produce Type I allergic reactions. It has been demonstrated that adrenalectomy results in accumulation of histamine in tissues,<sup>2</sup> associated with a reduction of histaminase, the enzyme that destroys histamine,<sup>3</sup> whereas administration of cortisol restores histaminase activity and causes depletion of tissue histamine stores. Also, corti-

## Chapter 8

### OTHER AUTOIMMUNE DISORDERS

For many years, it has been known that allergies are disorders of the immune response, but only relatively recently has it been recognized that rheumatoid arthritis and other collagen diseases are associated with a disturbance of the immune system, wherein the body develops antibodies or immune complexes that damage some of its own tissues. With recent advances in the techniques for recognizing disorders of the immune mechanism, a number of other clinical conditions have been found to be associated with autoimmune phenomena. These include hyperthyroidism with diffuse goiter (Graves' disease), chronic lymphocytic thyroiditis (struma lymphomatosa), diabetes mellitus, regional enteritis, and ulcerative colitis. The possibility of beneficial effects of physiologic dosages of glucocorticoids has been suggested in each of these prior to the demonstration of their autoimmune basis, so now it is even more desirable to determine the potential contribution of this therapy in their management.

#### HYPERTHYROIDISM WITH DIFFUSE GOITER

In 1930, Marine<sup>1</sup> postulated that Graves' disease was associated with adrenocortical insufficiency. Both conditions are characterized by enlargement of the lymph nodes associated with a relative lymphocytosis. When cortisone first became available, it is not surprising that therapeutic trials of its administration to patients with this disorder were made. Hill, Reiss, Forsham, and Thorn, in 1950<sup>2</sup>, reported that cortisone acetate, in doses of 100 to 200 mg per day for sixteen days, produced a decrease in serum protein-bound iodine and basal metabolic rate in a patient with Graves' disease. This group also reported that "following an initial exacerbation of clinical hyperthyroidism (manifested chiefly by an increase in basal metabolic rate) both ACTH and cortisone appear to suppress thyroid function in about one half of the patients with Graves' disease in this limited series." The clinical improvement in one patient given

## Chapter 9

# VIRAL INFECTIONS INCLUDING THE COMMON COLD, INFLUENZA, INFECTIOUS MONONUCLEOSIS AND SHINGLES

### THE COMMON COLD

Before cortisone became available, patients with chronic adrenal insufficiency were extremely vulnerable to stresses of any kind, and an ordinary respiratory infection often caused an acute collapse that was termed an "adrenal crisis." Patients had to be taken to a hospital and given intravenous saline and glucose as well as a parenteral adrenal cortical extract if that were available. After cortisone and cortisol were introduced, patients with Addison's disease were still cautioned regarding respiratory illness, and they were instructed that upon developing the initial symptoms of a common cold they should increase the dosage of glucocorticoid and phone their physician immediately. Concern regarding the occurrence of respiratory illness in such patients was enhanced by the knowledge that large doses of glucocorticoids could impair resistance to infection while masking the symptoms.<sup>1</sup>

It was, therefore, a finding of some surprise and considerable relief that months and then years passed with these patients consistently reporting that they had either no common colds or only very mild attacks. Most of these patients had no symptoms even suggestive of such disorders, but when symptoms did occur, a prompt increase in the replacement dosage of glucocorticoid was often followed by a disappearance of symptoms without recurrence when the dosage was returned to maintenance levels. During this time, other members of the patients' families seemed to have their usual quota of respiratory illnesses, so the absence of such illness in the patients could not be attributed to lack of exposure to the viruses.

An additional reassuring observation was that when patients with adrenal insufficiency developed respiratory infections, the increase in dosage of replacement glucocorticoid did not cause an increase in compli-

## Chapter 10

### MISCELLANEOUS CLINICAL CONDITIONS INCLUDING FUNCTIONAL HYPOGLYCEMIA AND THE CHRONIC FATIGUE SYNDROME

In previous chapters, clinical uses of physiologic dosages of cortisol or cortisone acetate in conditions in which their use has been either established or indicated for logical reasons have been discussed. I would now like to discuss other conditions in which, for various reasons, therapeutic promise also seems likely. In some of these conditions, the rationale for their use is also logical, but in others, at first glance, their use would seem contraindicated, at least on the basis of popular understanding of their actions.

#### HIRSUTISM

Although racial and familial factors contribute to the sensitivity of hair follicles to stimulation, the source of stimulation of coarse hair growth on the face, body and extremities is androgen. This is produced normally by the adrenals and testes and, under certain abnormal circumstances, by the ovaries. In addition, other tissues may be capable of converting precursors to androgens.

In a study of fourteen patients with hirsutism, Gibson and his associates<sup>1</sup> found evidence of abnormality of adrenal response to ACTH in all except three. In five patients, evidence suggested a partial deficiency of  $3\beta$ -hydroxysteroid dehydrogenase  $\Delta$  4-5 isomerase and in five others a partial deficiency of  $11\beta$ -hydroxylase. Also, in six patients an abnormally high increment of dehydroepiandrosterone relative to hydrocortisone was noted. Hence, patients with hirsutism as well as those with ovarian dysfunction have a high incidence of abnormal adrenal steroid metabolism.

Androgen excess causes increased hair growth on the beard area, trunk, and extremities and a thinning of scalp hair. Evidence of excessive androgen production is manifested by increased urinary excretion of 17-KS or by elevated plasma levels of testosterone or of DHEA sulfate.



## Chapter 11

### SUMMARY AND SPECULATION

These observations, spanning over forty-five years of experience with glucocorticoid therapy, obviously raise many additional questions. As a clinical investigator with limited research facilities, I have not been able to do more than scratch the surface of the potential of this type of treatment, but I hope the previous chapters have convinced the reader that cortisone or cortisol therapy can be safe and that the potential for this type of therapy is sufficiently great to warrant further study. Since this book was first published, few reports have answered any of the questions that were raised then in this chapter, but further experience and reports from other clinics have provided additional reasons for hoping that studies to answer at least some of these questions will be undertaken.

In conclusion, I would like to indulge in further speculation regarding a few of the possibilities raised in the previous chapters. Although some of these suggestions may seem rather remote and tenuous, they may provide a stimulus for future studies.

If the adrenal cortex does produce an anti-sodium-retaining factor as postulated in Chapter 3, it is possible that some cases of hypertension may result from a deficiency of this factor. Such cases would probably have low levels of renin because of the relative excess of sodium-retaining hormone, but the actual levels of sodium-retaining hormone might not be elevated. The possible sequence of events in the development of hypertension in such cases might be as follows: (1) a deficient intake of water relative to salt, producing an increased requirement for anti-sodium-retaining factor; (2) with prolonged maintenance of such a state, the ability to produce anti-sodium-retaining factor might become deficient or exhausted; (3) excessive sodium retention and hypertension would then result. The possibility that a relative deficiency of water intake might contribute to the production of hypertension should therefore be studied, as well as the possibility that an increased intake of water in addition to a decreased intake of sodium might be beneficial in the