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## Mild Adrenocortical Deficiency, Chronic Allergies, Autoimmune Disorders and the, Chronic Fatigue Syndrome: A Continuation of the Cortisone Story

W. McK. JEFFERIES

*Case-Western Reserve University School of Medicine, Cleveland, Ohio, USA (Correspondence to WMcKJ, 1208 Bixham Lane, Charlottesville, VA 22901, USA).*

**Abstract** -- The possibility that patients with disorders that improve with administration of large, pharmacologic dosages of glucocorticoids, such as chronic allergies and autoimmune disorders, might have mild deficiency of cortisol production or utilization has received little attention. Yet evidence that patients with rheumatoid arthritis improved with small, physiologic dosages of cortisol or cortisone acetate was reported over 25 years ago, and that patients with chronic allergic disorders or unexplained chronic fatigue also improved with administration of such small dosages was reported over 15 years ago, suggesting that these disorders might be associated with mild adrenocortical deficiency. The apparent reasons for the failure of these reports to be confirmed or mentioned in medical textbooks and the facts needed to restore perspective are reviewed, and the need for further studies of the possible relationship of a mild deficiency of the production or utilization of cortisol and possibly other normal adrenocortical hormones to the development of these disorders is discussed.

### Introduction

In most endocrine disorders varying degrees of deficiency of hormones are recognized, but deficiency of cortisol is classified only as Addison's disease or hypopituitarism, both relatively severe and relatively rare disorders. The possibility that milder degrees of adrenocortical deficiency, either primary in the adrenals or secondary to inadequate stimulation by the

pituitary or hypothalamus, might exist has not received much attention. Also, the possibility that patients with disorders that improve with administration of large, pharmacologic dosages of glucocorticoids, such as autoimmune disease and chronic allergies, might have mild adrenocortical deficiency apparently has not been considered since the introduction of this type of therapy 40 years ago. At that time methods of studying adrenocortical function were limited, and

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Kelley and Ely (1) summarized by stating:

*It appears that neither adrenocortical function nor steroid metabolism is completely normal in patients with connective tissue disease, but the abnormalities that exist may be quite subtle and difficult to demonstrate unequivocally. There is as yet no clear demonstration that these abnormalities are of significance in the pathogenesis of connective tissue disease; however, this remains a distinct possibility that deserves continuing investigation.*

Since no further evidence for such a possibility was reported, it was concluded that any abnormalities of adrenocortical function in these disorders were probably non-specific and unrelated to their etiology.

Although most clinical experience with glucocorticoids, other than in treatment of obvious adrenal deficiency in patients with Addison's disease or hypopituitarism, has involved administration of large, pharmacologic dosages with subsequent propensity for the development of undesirable or even alarming side-effects, beneficial effects of small subreplacement, safe, physiologic dosages of cortisol were initially reported in 1958 in the treatment of women with ovarian dysfunction and infertility (2). Some had evidence of excess androgen, such as acne or hirsutism, some had evidence of excess of estrogen, such as metropathia hemorrhagica, and some had ovarian dysfunction without evidence of either androgen or estrogen, but a majority of women in all groups improved with this therapy (3-9). As experience accumulated, patients with associated allergies or auto-immune disorders, including allergic rhinitis, bronchial asthma, and rheumatoid arthritis, reported improvement in these conditions while taking the small dosages even though such small dosages did not produce elevation of blood levels of cortisol above normal. These findings were presented at the annual meeting of the American College of Physicians in 1966 and published in 1967 (10), but in subsequent years no reports of attempts by others to confirm or extend them appeared.

In 1974, at the invitation of Dr Franz Ingelfinger, a chapter was contributed to *Controversies in Internal Medicine II* entitled, *Glucocorticoid Therapy: An Overmaligned Reputation With Untapped Potential Benefit* (11). In this chapter it was reported that, in addition to anti-allergic and anti-rheumatic effects, the administration of small, safe, physiologic dosages of cortisol 'appears to have anti-malaise and anti-fatigue

effects that warrant careful study', but still no attempts to extend or confirm these observations appeared.

In 1981, with encouragement of two authorities on adrenocortical function, a book was published in which the cortisone story was reviewed and further evidence was presented of impressive beneficial effects of small, subreplacement dosages of cortisol or cortisone acetate in patients with mild adrenal deficiency, either primary (low adrenal reserve) or secondary to inadequate stimulation by the pituitary. These beneficial effects were observed not only in patients with ovarian dysfunction but also in patients with rheumatoid arthritis, allergic rhinitis, bronchial asthma, Graves' disease, and diabetes mellitus (12). The book was published by a reputable medical publisher that has published much of the earlier work on cortisone, but still no subsequent reports of attempts to confirm or extend these studies appeared. The possibility that some patients with unexplained chronic fatigue (as in the chronic fatigue syndrome) might have mild adrenal deficiency, either primary or secondary, was also suggested. Such a possibility should not be surprising since fatigue is a characteristic early symptom of adrenocortical insufficiency, but this suggestion also apparently received little attention.

In the same year, 1981, Poteliakoff(13) reported that patients with chronic fatigue had lower blood cortisol levels than controls matched for age and sex. Still no attempts to confirm or extend these studies, or even any comments on them, appeared.

Because one of the most alarming effects of large, pharmacologic dosages of cortisol or its derivatives is impairment of immunity, and because small, physiologic dosages seemed to enhance immunity, a review of the medical literature on the relationship between normal adrenocortical function and immunity was made. This revealed that numerous investigators had reported evidence over the past 40 years that in physiologic amounts cortisol is essential for the development and maintenance of normal immunity in contrast to the well known harmful effects of large, pharmacologic amounts. This review was published in early 1991 (14), but it also apparently received relatively little attention.

The report of Demitrack et al later in 1991 (15) of evidence of low levels of cortisol in the blood of patients with the chronic fatigue syndrome without any attempt to treat these patients with a physiologic dosage of cortisol calls further attention to this unique situation in which a promising therapeutic approach to relatively common clinical problems apparently is overlooked or avoided.

### Background

How could such a situation occur? It has apparently resulted from a unique combination of factors, chief of which are:

1. At the time of the discovery of the dramatic clinical effects of cortisol in autoimmune disorders and allergies in 1949 and the early 1950s the normal production rate of cortisol was not known, nor were an optimum dosage, route or schedule of administration. It was found that a dosage of 100-300 mg cortisol intramuscularly, and later orally, daily was necessary to produce symptomatic benefit within 24 - 48 h. Later, when the normal production rate under unstressed conditions was found to be 18-20 mg daily, it was assumed that large, pharmacologic dosages were necessary to produce the dramatic therapeutic effects. The possibility that smaller dosages might produce beneficial effects more slowly but more safely was apparently not considered.

2. Because serious side effects often occurred with large dosages of the natural glucocorticoids, derivatives of cortisol or cortisone such as prednisone, prednisolone, triamcinolone, and dexamethasone were introduced, but, except for less tendency to retain salt and water, they possessed the potential to produce all of the other undesirable side-effects of large dosages of the natural steroids.

3. When patents expired on cortisone and cortisol, the more potent derivatives, whose patents persisted, were promoted more vigorously and the natural hormone tended to be forgotten. Package inserts no longer differentiated between physiologic and pharmacologic dosages of cortisol and it was implied that all of the grim side-effects might develop at any dosage level. The tendency by some to term all glucocorticoids 'cortisone' added to the confusion.

4. Most physicians practicing today are therefore under the impression that any dosage of cortisol can produce any of the serious side-effects that occur only with administration of large pharmacologic dosages of this normal hormone.

5. Reports documenting the safety and effectiveness of physiologic dosages of cortisol were published in reputable medical journals over 25 years ago (2-10), but computerized reviews of the medical literature, such as Medline, do not yet cover publications that remote, so few physicians today are aware of the existence of these reports.

6. One of the most alarming effects of pharmacologic

dosages was impairment of immunity, causing patients to become more susceptible to infections. This property has been used to help patients to tolerate tissue transplants, and hence has become quite widely known. It has even been suggested that the increased production of cortisol that occurs at the onset of infection may serve to limit the immune reaction from overshooting and hence would be consistent with the anti-immune effects of pharmacologic dosages (16), but a more likely explanation of this increased production is that of Ingle (17), which states:

*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.*

Evidence that cortisol impairs immunity only in large, pharmacologic dosages and that in physiologic amounts this hormone is essential for the development and maintenance of normal immunity has been reported by investigators over the past 40 years, but largely overlooked, as noted above (14). Most physicians are still not aware of this important difference between physiologic and pharmacologic effects of cortisol.

7. Before patients are given other hormones, tests of the function of the glands that produce those hormones are usually performed, but tests of adrenocortical function are seldom made on patients before the administration of glucocorticoids.

### Present status

These factors have led to a unique situation in which a normal hormone, one that is essential for life, has developed such a bad reputation that many physicians and patients are afraid to use it under any circumstances. In order to restore perspective, the following facts should be remembered:

1. Cortisol (hydrocortisone) is a normal hormone. Cortisone is converted to cortisol after absorption and hence has similar effects, provided there is no interference with this conversion. The more frequently used derivatives of cortisol or cortisone, such as prednisone, prednisolone, triamcinolone, methylprednisolone, and dexamethasone, have from 4-30 times the anti-inflammatory and glucocorticoid effects of corti-

sol, but, except for less sodium retention than the normal hormone, they have equally serious potential side-effects, and they are not produced by human or animal adrenals.

2. Cortisol is essential for life in humans; its most obvious effect is to promote gluconeogenesis to provide energy and avoid hypoglycemia in times when food intake is limited, but it also helps to protect against other stresses including the maintenance of normal immunity.

3. In the unstressed state, cortisol is normally produced on a diurnal pattern depending upon the sleep-wake schedule, the highest blood levels occurring after 7-8 h sleep and the lowest at bedtime.

4. Cortisol is a very dynamic hormone, with production and blood levels fluctuating rapidly from minute to minute, depending upon the degree of stress as well as upon diurnal variation. Because utilization as well as production varies with stress, blood levels may not always reflect the degree of stress or rate of production.

5. To evaluate adrenocortical function, blood ACTH, cortisol and a cosyntropin stimulation test under basal conditions are helpful. These studies should be performed on blood specimens drawn preferably in the morning before breakfast on patients on a normal sleep-wake schedule and not receiving any medication that might affect cortisol levels or adrenocortical function. 24h urinary free cortisol also contributes to the evaluation of disorders of adrenocortical function provided collections are made properly. One or more of these tests has been found to be abnormal in at least some patients with rheumatoid arthritis, chronic allergies, or unexplained chronic fatigue.

6. Normal ranges for blood cortisol levels and other tests of adrenal function have been determined on subjects who did not have obvious adrenocortical excess (Cushing's syndrome), or deficiency (Addison's disease), or panhypopituitarism, or any other apparent illness, and are rather broad. Hence they may include patients with mild deficiency or excess of cortisol. Also it must be remembered that resistance to cortisol may occur because of a defect in receptor function (18,19), so blood cortisol levels in the normal or even supranormal range do not exclude the possibility of symptoms associated with deficiency of cortisol effects.

7. If cortisol is administered to patients with mild primary adrenal deficiency in an amount less than a

full replacement dosage, there appears to be no summation effect beyond the reaching of an optimum level since patients receiving such dosages have not developed hypercortisolism. If they receive a full replacement dosage for a prolonged period, however, their adrenals might be suppressed sufficiently to impair further their resistance to stress. Patients with inadequate stimulation from the hypothalamus or pituitary have improved with subreplacement dosage, but because they do not have proper central control of production of cortisol, optimum treatment for this type of disorder needs further study.

8. Because a single intravenous injection of cortisol produces metabolic effects that last only about 8 h (20), an optimum schedule for administration of physiologic dosages orally for persistent effects probably should be at intervals of 8 h or less. Although medical texts recommend two or three times daily schedules of administration of cortisol to patients with adrenal deficiency, a three times daily schedule has been found to maintain afternoon blood levels of cortisol better than a two times daily schedule (21), and a four times daily schedule suppresses excessive adrenal androgen excretion better than a two times daily schedule (9). In the treatment of adrenal deficiency in our practice, a schedule of four times daily before meals and at bedtime has been found to have several advantages, including ease of adherence, less tendency to produce acid indigestion and, in dosages of 5 mg four times daily or less, failure to block normal diurnal variation (22). Taking milk or an antacid with the bedtime dose helps to avoid acid indigestion in susceptible patients. For a totally adrenalectomized patient under unstressed conditions, a dosage of 10 mg four times daily is adequate, and for lesser degrees of adrenocortical deficiency dosages of 7.5 mg, 5 mg, or 2.5 mg four times daily are satisfactory maintenance dosages, depending upon the degree of deficiency. Since over 2000 patient years of experience have been accumulated with such physiologic dosages (14), therapeutic trials with such dosages of cortisol would seem to be indicated in patients with chronic fatigue syndrome. Because these studies involve treatment of a hormonal deficiency, the normal hormone, not any of its derivatives, should be administered.

9. As with patients with severe adrenal deficiency, if a patient with mild adrenal deficiency has evidence of an active inflammatory process or infection, a larger dosage of cortisol, up to 20 mg four times daily, in conjunction with a suitable antibiotic or other type of therapy, is advisable, but when this condition is under control, the dosage of cortisol should be tapered to the

maintenance dosage (between 2.5-7.5 mg four times daily) over 2-4 days. Because cortisol is such a dynamic hormone, with increased production in times of stress, caution must be exercised not only to provide adequate amounts during the stress but also to avoid continuing the larger dosage too long, in which case hypercortisolism and hypokalemia with toxic effects may occur. Hypokalemia may also occur if cortisol is administered too rapidly intravenously, so, for parenteral administration the intramuscular route or a slow intravenous drip of 100 mg or less in normal saline over 8 h is safer. As with any medication, the administration of larger dosages must be employed judiciously.

10. During acute exacerbations, patients with allergies or autoimmune disorders need to take larger dosages of cortisol (20 mg four times daily is usually adequate), but as soon as symptoms are under control, the dosage should be tapered to a physiologic maintenance dosage. If this is not possible without a return of symptoms, a careful search should be made for obscure infection or other persistent source of stress that is preventing the return to a safe maintenance dosage.

11. Patients with mild primary adrenal deficiency treated with subreplacement dosages of cortisol may have slightly enhanced resistance to additional stress because the supplementary steroid has relieved some of the strain on their impaired adrenals and thereby provided slightly increased reserve capacity, but they seem to tolerate major stresses such as surgery or infections better if they are given supplementary cortisol just as patients with severe adrenal deficiency. Patients with adrenal deficiency secondary to inadequate stimulation from the pituitary or hypothalamus have been treated in a similar fashion with apparently satisfactory results, but further studies of optimum treatment of this type of disorder, as well as factors that contribute to its development, are advisable.

12. Since subreplacement dosages of cortisol do not produce an excess of glucocorticoid, they have not tended to promote the development of osteoporosis or any other undesirable side-effects that can result from administration of large, pharmacologic dosages. If patients have a deficiency of estrogen or androgen, replacement with physiologic dosages of these normal hormones is advisable.

## Discussion

The possibility that patients with chronic allergies or

autoimmune disorders might have mild adrenocortical deficiency should not be surprising since cortisol is the only known substance produced by the body that counteracts the symptoms of both of these disorders. Furthermore, it is well known that stress, either physical or emotional, often precedes the onset or exacerbation of symptoms of allergies, autoimmune disorders, or the chronic fatigue syndrome, and the adrenals are a major component of the body's defense against stress. A deficiency in the adrenals' response to stress might therefore in some way contribute to the development and progress of these disorders. Studies are also needed to determine why under increased stress one person might develop chronic allergies, another an autoimmune disorder, and another unexplained chronic fatigue. The familial tendency for the occurrence of these disorders suggests inherited factors of susceptibility.

The administration of any medication three 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 often produce some improvement, but for optimum benefit the four times daily schedule has been more helpful and easier to follow. Because the bedtime dosage of cortisol tends to keep the kidneys functioning during the night, some patients prefer to take a smaller dosage at bedtime, e.g. 2.5 mg, to avoid nocturia. Noticeable improvement usually occurs within a few hours of the first dose, and patients often describe a return of symptoms within a few hours of a missed dose. Occasionally improvement is not noticed until 10-14 days after treatment is begun, presumably because of a more severe underlying disorder, so patients should be cautioned regarding this possibility. After a remission occurs, if cortisol is stopped, a return of symptoms may develop after varying intervals, sometimes as long as several years.

Compliance is helped by giving patients printed instructions, briefly describing the reasons for the schedule, what to do if a dose is missed, and, in addition to contacting their physician, what to do if they develop a respiratory infection, G-I upset, influenza, or other illness (22). Patients have been treated with this schedule of cortisol or cortisone acetate for as long as 40 years without significant problems. Because some of these patients had ovarian dysfunction and infertility, and because continuation of small, physiologic dosages helped to protect against miscarriages, over 200 babies have been born to

women who continued these physiologic dosages through their pregnancies and sometimes during their postpartum (including nursing) periods with no evidence of harm to mothers or babies (22,23).

These findings were published, but the bad reputation of glucocorticoid therapy and the US Food and Drug Administration (FDA) regulation that requires that when a new use of a medication whose patent has expired is found, it should be treated as if it were a new medication has resulted in these reports receiving little attention. Such a regulation is obviously desirable, but without the protection of a patent, pharmaceutical companies have no incentive to undertake the extensive and expensive studies necessary to determine whether a medication is effective and safe for its recommended use for the general public. Without such studies, new uses cannot be promoted or advertised by the manufacturer, and without promotion or advertisement, a different therapeutic approach, especially one employing a medication that has achieved such a bad reputation as cortisone, is severely handicapped. It must be remembered, however, that 'The FDA cannot approve or disapprove of how a legally marketed drug is used by a physician in his practice. The agency approves of what the manufacturer may recommend about uses in its labeling (package insert) and advertising' (24). In other words, the physician has the ultimate responsibility of judging the suitability of a medication for his or her patient regardless of whether it is patented or whether its use is listed on the label or package inserts.

Further studies to elucidate these potentially important uses of this normal hormone are obviously advisable, and it might be questioned whether double-blind, placebo studies should be used for these. Such studies were initiated when the use of physiologic dosages of cortisol were found to be helpful in patients with some types of ovarian dysfunction (5), but the objective, as well as subjective, benefits were so clear, plus the finding that optimum dosage requirements varied within the physiologic range from patient to patient and sometimes from day to day in the same patient, that this type of study was soon abandoned. Studies of the effects of other normal hormones have not required, or even included, double-blind placebo studies, probably at least partly for these reasons. It should also be noted that the cause of the placebo effect has never been elucidated, yet double-blind, placebo studies continue to be considered essential by many for the evaluation of new therapies. Because the placebo effect is apparently related to expected improvement by patients, and because expected improvement implies a type of diminished stress, which

might in turn result in improved adrenocortical function, the possibility that the placebo effect might result from improved adrenocortical function should be considered.

The only significant problem that has developed related to therapy with physiologic dosages of cortisol arises not from the cortisol itself, but from the filler that is used in making the commercial tablets. Most, if not all tablets of cortisol or cortisone acetate contain lactose and cornstarch in the filler. In large, pharmacologic dosages, the quantity of cortisol is apparently sufficient to protect against lactose intolerance or allergy to corn, but small, physiologic dosages are not adequate to protect against such sensitivities in some patients, and a few have developed mild skin rashes or other evidence of a mild allergic reaction to the filler of the tablets. Such patients may need to take a pediatric liquid preparation of cortisol or capsules prepared with a non-allergenic filler. Because the pediatric preparation is too sweet for general adult use and specially prepared capsules are expensive, if these small physiologic dosages are more widely used, it is hoped that pharmaceutical companies will prepare tablets or capsules that do not contain lactose, apparently the more common offender, or cornstarch, or any other potentially allergenic substance.

There is therefore no reason to fear that physiologic dosages of cortisol will produce any of the harmful side-effects of pharmacologic dosages, and, in subjects with mild adrenal deficiency, either primary or secondary, who are not allergic to lactose or cornstarch, therapeutic trials with the normal hormone, cortisol, in physiologic amounts at proper intervals, should be made. Instead of the current custom of prescribing pharmacologic dosages of glucocorticoids on an empirical basis, if tests of adrenocortical function are made prior to initiating glucocorticoid therapy, mild degrees of adrenocortical deficiency might be identified that might be better treated with safe, physiologic dosages of the normal hormone, cortisol, a treatment that could be, and possibly should be, continued indefinitely, rather than being discontinued as soon as a remission occurs. If this is done, it is possible that many, if not all, patients with chronic allergies and autoimmune disorders will be found to have mild adrenocortical deficiency and hence would benefit from persistent administration of safe, physiologic dosages of normal adrenocortical hormone instead of being treated spasmodically with pharmacologic dosages of synthetic derivatives.

It should also be remembered that, in addition to cortisol, the human adrenal cortex produce aldosterone, androgens (chiefly dehydroepiandrosterone

[DHEA] and androstenedione) and estrogens (estrone and estradiol). Although effects of aldosterone and estrogens have been studied, the effects of physiologic dosages of DHEA and androstenedione in human subjects are largely unknown. The manner in which these adrenal hormones contribute to the welfare of the individual and possibly to protection against stress therefore also needs further study, especially since a low or absent excretion of DHEA has been found in some patients with rheumatoid arthritis (10). Such studies should be made with physiologic dosages on subjects who have a demonstrated deficiency of the hormone being studied.

### Conclusions

With the evidence that at least some patients with chronic allergies, autoimmune disorders and unexplained chronic fatigue, including the 'chronic fatigue syndrome', have mild adrenocortical deficiency, further studies of the above therapeutic approach seem indicated. Such studies will hopefully no longer be handicapped by misconceptions that have resulted largely from the unique combination of factors that have been discussed.

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