ecture, University of Bristol, for their help with the survey and discussion on the model.

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Clinical Endocrinology

Hypoadrenalism

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British Medical Journal, 1972, **1**, 679-681

The adrenal glands are made up of a cortex and a medulla. As no definite clinical condition has yet been ascribed to hypofunction of the medulla, this article will be confined to a discussion of adrenocortical deficiency.

Three main groups of hormones are secreted by the adrenal cortex. Firstly, the glucocorticoids. The secretion of these corticosteroids is controlled by the adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland. The most important glucocorticoid in man is cortisol (hydrocortisone), which also has some mineralocorticoid activity, and is normally secreted in amounts of about 20 mg daily. Glucocorticoids have many actions, such as stimulation of protein breakdown, antagonism to the action of insulin, and inhibition of the tissue response to injury.

The second main group are the mineralocorticoids. Aldosterone is the most powerful hormone of this group. Its secretion is largely independent of ACTH production, and is mainly controlled by the renin-angiotensin system and by the level of plasma potassium. Aldosterone stimulates the reabsorption of sodium in the distal renal tubules in exchange for potassium and hydrogen ion. The term corticosteroid is used to include glucocorticoids and mineralocorticoids.

The third group of hormones secreted by the adrenal cortex comprises the androgens. Though produced in relatively large amounts, the adrenal androgens are weak as compared with testosterone. They will not, for example, prevent the development of hypogonadism in men with testicular failure.

Adrenocortical Deficiency

Adrenocortical deficiency may be due to primary disorders of the adrenal cortex, diminished ACTH production in hypothalamic or pituitary disease, or suppression of the hypothalamic-anterior pituitary-adrenocortical axis by treatment with corticosteroids.

PRIMARY DISORDERS OF THE ADRENAL CORTEX

These may result in either generalized adrenocortical deficiency (Addison's disease) or in an isolated deficiency of one of the hormones produced by the adrenal cortex.

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Addison's Disease

Formerly most cases of Addison's disease were due to tuberculous destruction of the adrenal glands. With the decline in incidence of tuberculosis, about 60% of cases are now due to atrophy of the adrenal cortices, the remainder being caused by tuberculosis and a variety of rarer lesions affecting the glands such as carcinomatosis, amyloidosis, and fungal infections. Atrophic glands show infiltration of the cortex by lymphocytes, and the condition is thought to be an autoimmune disease. Not only does it occur in association with other conditions thought to be autoimmune in origin, such as pernicious anaemia and Hashimoto's thyroiditis, but circulating antibodies to adrenocortical tissue can be shown in the serum of such patients.¹ Addison's disease may also occur acutely from bilateral haemorrhages into the adrenal glands. This is sometimes seen in the newborn especially after a difficult delivery, or as a complication of fulminating infections such as meningococcal septicaemia (the Waterhouse-Friderichsen syndrome).

Clinical Features.—These are largely due to glucocorticoid and mineralocorticoid deficiency, the only definite sequel of adrenal androgen lack being loss or failure of development of body hair in women. Glucocorticoid deficiency results initially in anorexia, nausea, and vomiting and later in pyrexia, hypotension, and hypoglycaemia. Mineralocorticoid deficiency causes sodium depletion with dehydration and hypotension.

The condition is a potentially fatal one. It may present acutely with severe vomiting, abdominal pain, prostration, and shock (adrenal crisis). More commonly, however, there is a long history of general ill health, with weakness, anorexia, nausea, and loss of weight. Hypotension is found, often with appreciable postural hypotension, and there is abnormal brown pigmentation of the skin—involving, in particular, parts exposed to the sun, pressure areas such as the elbows, and the palmar creases, the nipples, and any scars. In addition there are often deposits of pigment on the buccal and conjunctival mucous membranes. This pigmentation is due to the overproduction of ACTH and the related anterior pituitary hormone melanocyte stimulating hormone (MSH), resulting from the low levels of circulating cortisol. There may also be patchy areas of loss of skin pigmentation (vitiligo). Mental changes occur and, paradoxically, a transient psychosis is sometimes precipitated by treatment.

Investigations.—Mineralocorticoid deficiency results in low levels of plasma sodium and raised levels of plasma potassium and urea. Glucocorticoid deficiency commonly causes electro-

cardiographic changes with flattening and sometimes inversion of the T waves, which revert to normal following treatment. X-ray films show bilateral adrenal calcification in cases of tuberculous Addison's disease. Glucocorticoids enhance a water diuresis and therefore failure of the normal excretion of a water load can be used as a test for adrenocortical deficiency. (A normal person excretes over 75% of a one-litre water load in four hours, whereas a patient with Addison's disease will excrete less than 50% in this time.)

Measurement of plasma or urinary corticosteroids is necessary to establish the diagnosis with the certainty that is essential before beginning life-long treatment. The urinary and plasma corticosteroid levels are usually low when measured basally. Nevertheless, the pathognomic finding is their failure to show a rise after the administration of ACTH or tetracosactrin. These may be given either intravenously or intramuscularly and values for a normal response, which virtually excludes the diagnosis, are well established.² In an adrenal crisis treatment is urgently required and should not be delayed for the sake of investigations, as it does not invalidate the result of a subsequent stimulation test if this is done within a few weeks. The treatment should be changed to a maintenance dose of a highly potent glucocorticoid which does not affect the corticosteroid measurements, such as dexamethasone, and the test done in the usual way.

Treatment.—An adrenal crisis is a medical emergency and requires intensive therapy with intravenous saline and glucose, and high doses of corticosteroids. Intravenous cortisol hemisuccinate is the treatment of choice, in amounts of 200–400 mg in the first 24 hours. Parenteral cortisone acetate should not be used as it is not effective fast enough. The doses of cortisol usually provide sufficient mineralocorticoid effect as well. If additional mineralocorticoid is required intramuscular desoxycorticosterone acetate (DOCA) can be given in doses of 5–10 mg. A search should be made for factors precipitating the crisis which may require independent treatment. After the first 24–48 hours treatment can be gradually reduced to maintenance doses of corticosteroids.

A usual maintenance dose is 20–30 mg of cortisol daily, which is given as 20 mg in the morning and 10 mg in the evening to reproduce the normal diurnal rhythm of cortisol secretion. Additional mineralocorticoid is usually required, and a convenient oral preparation is 9- α fluorohydrocortisone (fludrocortisone), 0.05–0.2 mg daily. Treatment is monitored by measuring changes of body weight, blood pressure, and plasma electrolytes. Excessive mineralocorticoid treatment produces oedema, hypertension, and potassium deficiency. All patients should carry a card with details of their treatment, and be instructed to double or treble the dose of cortisol in an intercurrent illness. A common problem is vomiting from a gastrointestinal infection making the patient unable to keep down his tablets. Cortisol deficiency may then supervene on the original illness, and large doses of parenteral cortisol may be required. In patients with tuberculous Addison's disease corticosteroid treatment sometimes activates latent tuberculosis, and so in them a standard course of twelve to eighteen months' anti-tuberculous chemotherapy should also be given.

Isolated Defects of Adrenocortical Hormone Secretion

The most common example of this is the adrenogenital syndrome (congenital adrenal hyperplasia), in which there is a congenital deficiency of one of the enzymes concerned with cortisol synthesis. A compensatory increase of ACTH production occurs, to try and maintain normal levels of circulating cortisols, which also results in the production of excessive amounts of adrenal androgens. Such patients present either in infancy or childhood with virilism, or in infancy with acute salt depletion, probably from associated aldosterone deficiency. Treatment of this salt-losing form is with intravenous fluids

and glucocorticoids and mineralocorticoids. They, and the children with virilism, require permanent maintenance glucocorticoid therapy, which makes up for the defect of cortisol synthesis and inhibits excessive ACTH secretion.

DIMINISHED ACTH PRODUCTION

Hypoadrenalism occurs as part of the syndrome of hypopituitarism. Together with thyroid deficiency (from loss of TSH secretion), adrenocortical deficiency occurs relatively late in the progression of hypopituitarism, while loss of growth hormone and the gonadotrophic hormones tends to occur early. Hypoadrenalism from diminished ACTH production largely affects glucocorticoid secretion, the production of mineralocorticoid being relatively normal. Such patients therefore manifest the features of glucocorticoid deficiency already discussed. There is no salt depletion but the plasma sodium concentration is often low from water retention due to impairment of the ability to produce a water diuresis. This may result in the condition of water intoxication—with drowsiness, mental confusion, and ultimately fits and coma.

Investigations.—The urinary and plasma corticosteroid levels are usually low, but the adrenal cortices are capable of responding to ACTH or tetracosactrin, though usually in a slow stepwise fashion as they have previously been inactive. There are other investigations, such as the insulin tolerance test and the metyrapone test, that can be used to assess the function of the whole hypothalamus-anterior pituitary-adrenal cortex system. There is also likely to be clinical and test evidence of other pituitary hormone deficiencies, and the cause of the condition may be apparent from finding an abnormal pituitary fossa in the skull x-ray film, indicating the presence of a pituitary tumour.

Treatment.—Treatment is the same as for Addison's disease except that mineralocorticoids are not required. Additional endocrine treatment will be needed for any other hormone deficiencies.

SUPPRESSION OF HYPOTHALAMIC-ANTERIOR PITUITARY-ADRENOCORTICAL AXIS BY CORTICOSTEROIDS

This is the commonest cause of hypoadrenalism because of the large number of conditions treated with corticosteroids. The risk of suppression is related to the dose and duration of glucocorticoid therapy. Doses of, or exceeding, 30 mg of cortisol daily or its equivalent (see Table) produce this effect, and smaller

Comparative Potencies of Different Glucocorticoids⁴

Glucocorticoid	Equivalent Doses (mg)
Cortisol	25
Cortisone	20
Prednisone	5
Prednisolone	5
Methyl prednisolone	4
Triamcinolone	4
Betamethasone	0.75
Dexamethasone	0.75

doses may also do so if given for prolonged periods. Every attempt should be made to prevent such suppression and the dose of glucocorticoid should be kept to the minimum required to control the underlying disease. It has been suggested that alternate day glucocorticoid therapy, in which the total dose for two days is given as a single dose on alternate days, is less likely to produce adrenocortical suppression than conventional daily treatment in divided doses.³

Adrenocortical deficiency arises in these patients either

because corticosteroid treatment has, for some reason, been omitted, or because the dose has not been sufficiently increased during an intercurrent illness. It can also arise during an attempted withdrawal of glucocorticoid therapy. The clinical features are those of glucocorticoid deficiency, and treatment is with high doses of cortisol, which usually have to be given parenterally.

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Second Opinion, Please

Asthma and a Lump in the Breast

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British Medical Journal, 1972, 1, 681-682

Mrs. C. D. Date of Birth 25 June 1929

Entries on Medical Record Card E.C.8

- 7 January 1969: Mild cough. Non-productive. 10 days. Benlyn Expect.
 15 January: No improvement. Worse at night. Slight dyspnoea during day. Tabs. Ffranol.
 29 January: Spasmodic attacks of coughing. No sputum. O.E. scattered wheezy rhonchi. Diagnosis bronchospasm. Syrup Ventolin.
 13 February: Insomnia through attacks of spasmodic coughing and wheezing. Asthma?
 For Hb, E.S.R., and urine examinations, please sister.

Conversation Between Partners (14 February)

- C.H.G.: John, would you have a look at Mrs. C.D. I can't make her out, I have been treating her for five or six weeks for a spasmodic cough and I think she is developing asthma.
 J.W.S.: How old is she, Charles?
 C.H.G.: Forty-two. You will see from the thinness of her record card she has rarely seen us. She had one child about 14 years ago, but that was stillborn.
 J.W.S.: It is a bit unusual to develop asthma this late in life. Are there any precipitating factors?
 C.H.G.: What do you mean?
 J.W.S.: Infection, allergy, any stress in the family. Is she a worrying type of person?
 C.H.G.: No, she is rather a neat, tidy, good looking woman with a very good husband. By the way, I have asked sister to do some routine tests.

Entries on Medical Record Card E.C.8

- 16 February: Hb. 78%; E.S.R. 42 mm in the first hour; urine N.A.D.
 20 February: Charles, I can find very little wrong here and confirm all your findings. There must be an allergic factor. She tells me she acquired a budgerigar in December. I have asked sister to do Bencard skin testing.
 21 February: Skin tests; all negative except feathers.
 In view of the above I suggest specific desensitization—J.W.S.

Tamworth, Staffs

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Conversation Between Partners

- J.W.S.: By the way, Charles, did you start Mrs. C.D. on a desensitization course against her budgerigar?
 C.H.G.: No. I don't really think that is the answer. She is now producing yellow sputum and I have put her on tetracycline for two weeks, and she seems a great deal better.
 J.W.S.: You know, I think you ought to have another x-ray and an E.C.G. done.
 C.H.G.: Very well, but all these investigations are a bit beyond me. I'm rather old-fashioned. Actually, a mass radiography survey was done in November on her and that was negative.

Entries on Medical Record Card E.C.8

- 23 March: X-ray chest: no gross pulmonary lesion. Slight increase in hilar shadow and some peribronchial opacity.
 E.C.G.: normal except for increase in QRS complex in lead 2.
 15 April: Night visit. Asthma attack. i.v. aminophylline 5 ml.
 2 May: Evening call. Bronchospasm. Tabs. Amesec.
 3 May: Call by sister; much improved.
 4 May: Charles, I suggest putting this patient on prednisolone 5 mg t.d.s. It's worth the risk. I should reduce the dosage slowly but increase it if she gets an intercurrent infection. I suggest also putting the budgerigar in the front room.—J.W.S.

From Laurel House, Tamworth, to Practice Health Visitor (4 July)

Would you be good enough to pop in and see Mrs. C.D. She has had some kind of asthma for the past five months, and I was called out once again at 10 p.m. Last night she was wheezing terribly when I got there and the whole family were in a state of excitement. I noticed that as I sat down and talked she gradually got easier, although maintaining she felt terrible. I spent some time inquiring about causes of stress—that is, husband troubles, work, or neighbours—but her sister indignantly told me that I should be ashamed of myself for suggesting all was not harmonious in the home. She assures me they have never had any trouble in their married life.

From Practice Health Visitor to Laurel House, Tamworth (5 July)

I went in to see Mrs. C.D. as you asked and there certainly does not seem to be any family troubles whatsoever, and it