REFRESHER COURSE FOR GENERAL PRACTITIONERS

ADDISON'S DISEASE

BY

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Thomas Addison, of Guy's, when he read his paper before the South London Medical Society in 1849 (at the age of 56), or published his more significant monograph *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules* in 1855, could hardly have fully realized that he had founded the science of clinical endocrinology or that the isolation and synthesis of the many vital hormones secreted by the adrenal gland would occupy some of the best biochemists of the New and the Old World in the middle of the twentieth century. This brief revision article, however, is limited to the disease of adrenal insufficiency, so appropriately called Addison's disease, and so adequately described in clinical and pathological terms by Addison in 1855.

As to the pathology of Addison's eleven cases, six showed destruction of the adrenal glands by tuberculosis and three by secondary carcinoma, one only showed atrophy and fibrosis, and one a carcinomatous nodule blocking the adrenal vein. A more extensive series of cases shows bilateral tuberculosis to be the cause in some 70% of cases, idiopathic atrophy or necrosis in 25%, and malignant destruction and other causes to be comparatively rare. Pulmonary tuberculosis is only rarely complicated by Addison's disease; but glandular or bony or genital tuberculosis not infrequently has been present some years previously and may be clinically healed before the onset of adrenal insufficiency. There is no clue to the cause of the non-tuberculous atrophy, which is therefore called idiopathic, but it is not unreasonable to postulate a virus infection comparable to the influence of the virus of mumps on the testicles.

Essential Hormones Secreted by Adrenal Cortex

It is generally held that the practitioner is not much concerned with physiology and biochemistry, and I would agree that his busy life limits his interest in the more technical and abstract aspects of these subjects. Nevertheless, in endocrinology, if not so much in other branches of medicine, the fundamentals of these subjects throw considerable light on symptomatology, diagnosis, and treatment. I will therefore consider briefly the essential hormones secreted by the adrenal cortex, the medulla playing little or no part in the deficiency disease of the adrenals.

1. Deoxycortone, or "sodium hormone."—This controls the plasma concentration and excretion of sodium, chloride, and potassium. In the adrenalectomized animal, or the patient with Addison's disease, there is increased urinary excretion of sodium and chloride and retention of potassium, so that the plasma sodium and chloride concentrations tend to be low and the plasma potassium tends to be high. The injection of deoxycortone corrects these changes in mineral metabolism.

2. The corticosterone (11-oxysteroid) group or diabetogenic anti-insulin hormones.—The adrenalectomized animal, or the patient with Addison's disease, manifests a tendency to hypoglycaemia, more evident under conditions of fasting or stress, and in contrast a patient with an adrenal tumour secreting an excess of 11-oxysteroids, as in Cushing's syndrome, may show clinical diabetes mellitus.

3. The adrenals secrete androgens, oestrogens, and progesterone, which hormones may be grouped together as sex hormones.

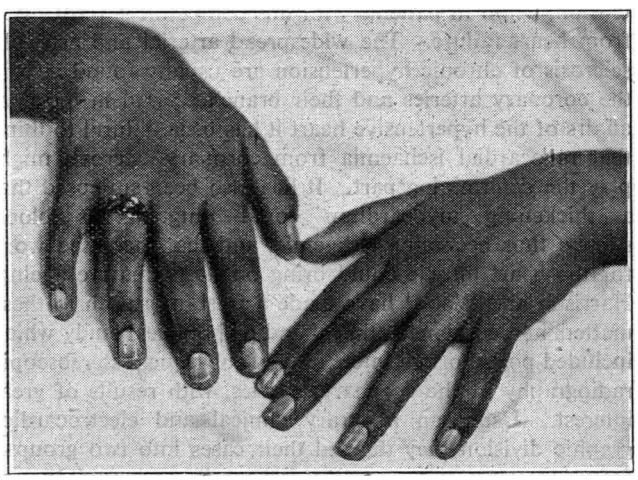
4. When these groups of hormones have been extracted there remains an amorphous fraction, which is more potent weight for weight than the crystalline hormones in maintaining the life of adrenalectomized animals and which also favourably influences renal function.

5. Knowledge is accumulating about an adrenal fat-controlling hormone, excess of which causes a general deposition of fat in the tissue; in contrast the tissues of adrenalectomized animals are almost devoid of fat.

6. Pigment-controlling hormone which seems to have some co-ordinating action with pituitary, in so far as the excessive deposition of melanin in the skin is very marked in Addison's disease, but is slight or absent in Simmonds's disease, in which, however, the adrenal cortex is atrophied and is functioning poorly as judged by carbohydrate and mineral metabolism abnormalities. It is difficult to study the pigment factor in adrenalectomized animals.

Clinical Manifestations of Addison's Disease

The main features are muscular weakness and tendency to fatigue, loss of appetite, loss of weight, low blood pressure, and pigmentation of the skin and mucous membranes. Anorexia may be particularly marked with fatty foods, and may be associated with nausea, vomiting, and intermittent diarrhoea. Abdominal pain and colic are met with



Extreme pigmentation of the hands in a girl of 18 with acute Addison's disease, showing excessive deposition of melanin especially on the dorsal aspect of the finger-joints. (This illustration, from the author's *Major Endocrine Disorders*, is reproduced by permission of the Oxford University Press.)

and the diaphragm may be irritated by the underlying diseased adrenal, with resulting costal or referred shoulder pain. Hiccup, yawning, conjunctivitis, grimaces, involuntary cries, negativism, contrariness, and apathy constitute an interesting group of associated symptoms of clinical and diagnostic significance. Sensitivity to cold, with curling up under the bedclothes, and a subnormal temperature are features which may be associated with a low basal

metabolism. Menstruation may be quite normal, and pregnancy may occur, but amenorrhoea and impotence are met with.

Hypoglycaemic symptoms may or may not be present, but in some patients hypoglycaemic coma can come on with great suddenness and lead to death if undiagnosed. The pigment is an increase of the normal melanin in the basal layers of the epidermis, and is found in the skin exposed to air or sunshine, for example, on the face and backs of hands (see Figure), and to pressure or friction, for example, in the axillae, groin, and under the waistband. Pigment may also be present on the gums and lips and in the buccal and anal mucous membranes. In a fair patient, who in health tends to go red rather than brown in summer, pigmentation may be slight or absent. The same is true when the adrenal insufficiency is of acute onset. Pigmentation may occasionally be of leucodermic type, as in one of Addison's patients, and in a case of mine that came to necropsy. This is probably explained by adrenal insufficiency being superimposed on, and accentuating, a previous or coincident tendency to leucoderma.

Diagnosis

Addison's disease may occur at any age, but is very rare before puberty or after 60. It is most frequent in the second and third decades. Diagnosis is not difficult if the above symptomatology is met with, but dramatic missed diagnoses may be seen if the disease is not kept in mind. Thus in one teaching hospital a man aged 36 was operated upon for a supposed perforated duodenal ulcer and nothing was found. At necropsy both suprarenal glands were seen to be destroyed by tuberculosis and pigment was obvious on the skin and buccal mucous membranes. In crisis the picture of Addison's disease closely resembles surgical shock, and it was this resemblance that stimulated Loeb to the discovery of the salt loss in Addison's disease. An opposite but less serious error was the diagnosis of Addison's disease in a case of normal early pregnancy associated with physiological pigmentation in a dark-skinned person and some vomiting and malaise. This was more easily understandable, since there is an extra demand upon the adrenal cortex in pregnancy, and some cases of Addison's disease are first revealed by a pregnancy, and may temporarily clear up for a while after it.

Addison's disease may be very acute and severe and quickly fatal, or may be mild and chronic, one such patient being alive and well after eight years, the only treatment being moderate amounts of salt by mouth. Such mild chronic cases may nevertheless be associated with deep and intense generalized pigmentation. In a crisis, not only is the blood pressure very low and the pulse almost imperceptible, but there is considerable haemoconcentration and collapse of the veins, which latter may be very difficult to enter with a needle, making venous blood difficult to withdraw. In the more chronic phases blood pressure may be normal, or occasionally high, if there has been a pre-existing hypertension. Similarly the fasting blood sugar may be normal, though it tends to fall in crisis.

In Simmonds's disease there is also weakness, anorexia, loss of weight, low blood pressure, low blood sugar, and subnormal temperature. Pigmentation is absent or mild and patchy. Amenorrhoea in Simmonds's disease is almost invariable, and complete loss of pubic and axillary hair is the rule, to which, however, there are definite exceptions. Bradycardia and a pronounced lowering of the basal metabolic rate in the absence of crisis favour a diagnosis of Simmonds's disease. If the condition has followed parturition associated with haemorrhage or infection, or if there is evidence of a craniopharyngioma or chromophobe adenoma of the pituitary, the diagnosis is Simmonds's disease and not Addison's disease. For all practical purposes, and excluding racial pigmentation, mucous membrane pigmentation is pathognomonic of Addison's disease, but is by no means an essential feature.

As to biochemical data, normal plasma or serum values are: sodium, 320–350 mg. per 100 ml. (or 141 milli-equivalents); chloride, 355 mg. expressed as Cl or 585 mg. expressed as NaCl per 100 ml. (or 100 milli-equivalents expressed either as Cl or NaCl); potassium, 18 to 20 mg. per 100 ml. (or 5 milli-equivalents). A milli-equivalent is milligrams per litre, divided by the atomic weight for monovalent elements. In Addison's disease, particularly in crisis, the sodium may be, for example, 290 mg., the chloride (as NaCl) 485 mg., and the potassium 28 mg. per 100 ml. In the more chronic phases a normal mineral chemistry does not exclude Addison's disease and the sodium values are more likely to be lowered than the chloride values. As to the potassium, this is elevated only in severe adrenal insufficiency. The blood urea is raised appreciably in severe insufficiency or crisis.

The Kepler test is a quotient arrived at by the study of blood and urine chloride and urea concentrations and water excretion. In Addison's disease the quotient is less than 30 and usually less than 15. (Blood for estimation of minerals must be taken into a special "pyrex" tube and the serum separated immediately after clotting; it is not essential to collect under liquid paraffin.)

The blood count may show a leucopenia, relative lymphocytosis, and eosinophilia. This eosinophilia is rarely depressed more than 30% by the injection of 0.3 mg. of adrenaline subcutaneously, or 25 mg. of A.C.T.H. intramuscularly, and is usually not affected at all by such injections, there being no adrenal cortex left that can respond. The measurement is made before and four hours after the injection, and is suggested by Thorn as an additional diagnostic test, patients with normal adrenals showing a consistent 50% fall in eosinophils. The sedimentation rate is often raised whatever the pathological lesion of the adrenals may be. The urinary 17-ketosteroids are decreased, particularly in women.

Treatment

The logical treatment of adrenal insufficiency is replacement therapy with an adrenal extract which contains all the essential hormones, and such therapy must be continued for life as with insulin for diabetes mellitus. Unfortunately available extracts are neither comprehensive in their content nor concentrated enough to make therapy completely adequate. Nevertheless, cortical extract can be used with good clinical results, the average patient requiring some 10 ml. daily, injected intramuscularly. With more severe insufficiency as much as 30 ml. is required daily. These extracts have some action upon both mineral and carbohydrate metabolism. Occasionally a patient reacts allergically to such injections, either locally or generally, and continued therapy is not possible. Where there is some pain at the site of injection, the addition of 0.2 ml. of 2% procaine hydrochloride to the contents of the syringe is helpful.

Deoxycortone acetate influences only mineral metabolism and does not correct hypoglycaemia, at least directly. Nevertheless, by increasing well-being and appetite it may be useful even in this direction also. It is prepared in ampoules of 5 mg. and 10 mg. in 1 ml. of oily solution. The average patient requires 5 mg. daily injected intramuscularly, and

because of the small bulk patients prefer this to cortical extracts. Further, deoxycortone can be implanted subcutaneously, one tablet of 100 mg. being used for each 1 mg. of injected material. Thus the average patient receiving 5 mg. daily would have implanted 500 mg. of deoxycortone tablets (five tablets of 100 mg. each). Before calculating this dosage it is advisable to maintain the patient for several weeks on injections, as the ultimate daily maintenance dosage may be appreciably less than the initial dosage.

As the effects of overdosage are severe and potentially fatal, I subtract 100 mg. from my calculated implantation dose, and for further safety I rarely do an initial implantation of more than 300 mg. The implantation calculations I have given are the ones I initially recommended, but are only half of the equivalents given by an American authority.

The effects of overdosage are seen both with the injection method and with the implantation method, but the former is much easier to correct than the latter, which necessitates removal of tablets. Overdosage leads to excessive retention of fluid and sodium, with increased excretion of potassium and low potassium serum concentration, resulting in weakness and paralysis of muscles, including the cardiac muscle. Other characteristic manifestations are superficial oedema of face and limbs, crepitations in the lungs, and enlargement of the heart, with or without pericardial effusion. The oedema, however, may not be conspicuous, and the excessive weakness or paralysis may be wrongly regarded as due to inadequate treatment. The blood chemistry may be deceptive in that the sodium and chloride may be normal, but the serum potassium is always low—for example, 12 mg. per 100 ml. Hypertension may be present initially with excessive fluid retention, but with cardiac failure this gives place to hypotension. Apart from the oedema of the cardiac muscle, multiple foci of necrosis in the heart have been found at necropsy. Electrocardiographic changes, with low serum potassium, are low-voltage QRS complexes, lowering or inversion of the T waves, depression of the S–T segment, and prolongation of the QRS interval. Occasionally some patients show a more insidious chronic dry hypertension with this treatment, but in the absence of the other features this is not usually important and may tend to correct itself. (Such low potassium concentrations are also met with in diabetic coma treated with intravenous salines and glucose, in infantile diarrhoea, and in surgical operations where there have been diarrhoea, intestinal drainage, and/or excessive intravenous saline.)

The best treatment of overdosage in Addison's disease is removal of the implanted tablets, but as a preliminary emergency measure 100 ml. of 2% potassium chloride may be injected intravenously. If the dosage is properly calculated, however, implantation therapy is excellent, and since the effects last some eight months many patients prefer it to all other methods of treatment. As the effect of therapy wears off the administration of salt by mouth may permit the postponement of further implantation from the sixth to the tenth month. Salt is also given by mouth without any other therapy in mild cases of Addison's disease. The dosage is up to 12 g. daily (three teaspoonfuls) in divided doses in a tumblerful of water or lime juice, or with porridge or potatoes. A mixture of sodium chloride, phosphate, citrate, and bicarbonate may prove more palatable. Sodium chloride in 1-g. capsules can also be obtained. Additional salt should be given with caution if deoxycortone is also used, for fear of excessive water and salt retention.

Such overdosage effects of deoxycortone as described above are not usually met with if cortical extracts are used, especially if the daily dose of the latter is less than 20 ml. In the U.S.A. a concentrated lipoid-extract of hog's adrenals has been prepared which is five times as potent as an aqueous extract, particularly in regard to the effect on carbohydrate metabolism. The extract is not yet available in this country. Linguets of adrenal cortical extracts for dissolving under the tongue, as prepared for some American investigators, have proved adequate for prolonged therapy, but those available to me have not proved sufficiently constant in action. Testosterone or methyl testosterone is indicated where the urinary 17-ketosteroids are less than 5 mg. a day, but if implanted the augmentation thereby of the sodium and fluid retention of deoxycortone must be reckoned with. In crisis, or in the acute phase of adrenal insufficiency, treatment differs from the more chronic phase only in its intensity and the advisability of using both cortical extract and deoxycortone. Intravenous saline is called for if the patient has been allowed to become very collapsed, and it is often necessary to cut down on a vein, If severe hypoglycaemia is suspected—and this is more likely in a patient who has been treated previously with deoxycortone and not cortical extract—intravenous glucose is necessary.

Course and Prognosis

Even if adequately treated, as judged by biochemical data, the more severe cases of Addison's disease lead a precariously balanced existence, and are liable to go into crisis, with or without a precipitating cause—for example, infection, trauma, strain—and to have phases of hypoglycaemia, sometimes acute and dramatic. They tend to lose weight and body fat over a period of years, and the pubic and axillary hair may become thinned. Apathy and inertia are not infrequent, and there is often a sensitivity to cold and infection. Nevertheless, one of my patients had two successful pregnancies under treatment, and is a good mother to the children and an efficient wife. Another seemed to have a sustained remission during her climacteric, and then partially relapsed again.

BRONCHOSPIROMETRY

SEMON LECTURE BY DR. PAUL FRENCKNER

The annual Semon Lecture was delivered at the Royal Society of Medicine on November 2 by Dr. PAUL FRENCKNER, of the Karolinska Institutet, Stockholm. His subject was "The Development and Present Use of Bronchospirometry." Dr. E. R. BOLAND, Dean of the Faculty of Medicine, London University, was in the chair.

Dr. FRENCKNER began with a tribute to Sir Felix Semon, whom he described as one of the greatest laryngologists of all time, with whose work and discoveries, he said, he had come into contact in his own first laryngological studies, on paralysis of the vocal cord, 25 years ago.

Dr. Frenckner described his first experiments in 1929 in what he called bronchial catheterization. His purpose was to work out a method of clinical examination with which it would be possible to judge the function of each lung separately, in the same manner as it was possible to form an opinion on each kidney by ureteral catheterization. By bronchial catheterization was meant the passing of a tubular instrument, flexible or rigid, into a predetermined bronchus, an airtight closure between the bronchial wall and the instrument being obtained by means of a special fixture at its distal end, so that it was possible to transmit to or from the area of distribution of the airway in question a gaseous or fluid substance for diagnostic or therapeutic purposes. In association with Jacobaeus and others in Sweden the concept of bronchospirometry was created. Various instruments had been used during the development of the investigation, but the work took a big step forward with the introduction of Carlens's