ENDOCRINES IN THEORY AND PRACTICE

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ADDISON'S DISEASE AND SUPRARENAL INSUFFICIENCY

BY

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Addison's Disease

Since Addison described in 1855 the syndrome which is due to destruction of the suprarenal glands little has been added to knowledge of the essential pathology of the condition. The cortex, but not the medulla, of the suprarenals is necessary for life, and the fundamental cause of death is deficiency of cortical secretion. Lack of cortex is responsible for most of the clinical findings, but it is probable that deficiency of medullary secretion also plays a part in the production of features such as pigmentation, hypotension, and hypoglycaemia.

Aetiology

Addison's disease may occur at almost any age, but it is very rare in children; its incidence is most frequent between the ages of 30 and 50. It is said to be more common in men than in women. In most cases the condition is caused by tuberculosis of both suprarenals, usually associated with tuberculosis elsewhere (for example, in the lungs), although this is often clinically latent. According to different reports tuberculosis accounts for 70 to 90 per cent. of cases of Addison's disease, the bulk of the remainder being due to simple atrophy of the glands. In this country, however, atrophy is probably as common a cause as tuberculosis, and is more likely to be responsible for the disease in women aged 35 to 45 and at the climacteric. Other but rare causal conditions are syphilitic fibrosis, amyloid disease, and, very rarely, malignant disease.

Clinical Features

Some authors describe three stages: (1) the early or latent phase, which clinically cannot be recognized as Addison's disease and may be diagnosed as "influenza"; (2) the classical syndrome; and (3) the terminal phase, which presents the features of collapse. The symptoms which may arise during the second stage are manifold. Among them may be mentioned asthenia, faintness, insomnia, restlessness, anorexia (especially aversion to fat), nausea, vomiting, intermittent diarrhoea associated with intervals of constipation, epigastric discomfort, abdominal pain and tenderness in the loins, yawning, hiccups, pigmentation, conjunctivitis, psychological changes (especially depression), loss of weight, scanty menstruation or amenorrhoea, loss of libido, and impotence.

Early symptoms may be anorexia, nausea, vomiting, and epigastric discomfort, or depression, asthenia, insomnia, and loss of weight, or pigmentation only, which in very chronic cases may persist for many months before any other manifestations present themselves. In children gastro-intestinal disturbances are prominent.

The pigmentation appears chiefly in those parts of the skin which are continuously exposed to sunlight, in those subjected to more or less continuous pressure by articles of clothing, and in those normally more heavily pigmented than the rest of the body—for example, the axillae, the

areola of the nipples, the linea alba, and the genital and anal regions. It also occurs characteristically in the mucous membrane of the mouth, where it has a bluish tinge—especially at the inner aspect of the cheeks, tongue, palate, and gums—and in the skin of the labia, but not in the rectum or vagina. It is often seen round the edges of scars but not in the scar tissue itself, and is often associated with dark brown or black pigmented spots or freckles, and occasionally with leucoderma. In acute cases pigmentation is frequently absent.

These patients have a marked sensitivity to cold and drugs, a poor resistance to operations and shock, and a susceptibility to infection. The body temperature is usually subnormal. The heart may be diminished in size, the sounds faint and distant, and the pulse of poor volume. The systolic and diastolic blood pressures are almost always low, the systolic being below 90; in the early stages, however, the blood pressure may be normal. The urine may contain a slight amount of albumin and occasionally casts.

In the chronic cases remissions and relapses occur. During a remission, which may last for weeks, months, or even years, the blood pressure commonly remains low, although the other features of the disease improve considerably. Patients are very liable to crises, which are heralded by increasing weakness, psychical disturbances, nausea, vomiting, deepening of the pigmentation, and fall of temperature and blood pressure. In a severe crisis the asthenia and vomiting are extreme, there is marked loss of weight, the systolic blood pressure may be below 70, and there may be suppression of urine; in other words, the patient is suffering from collapse and dehydration, which some observers consider responsible for the symptoms. Death usually takes place in one of these crises. They may be precipitated by undue exertion, exposure to cold, a slight operation or an infection, or they may come on for no apparent reason, in which case they may be due to further damage to the suprarenal cortex. The duration of life is longer and severe crises are less frequent in those with marked pigmentation, little asthenia, and few gastro-intestinal symptoms. The most important single prognostic index is body weight; those who eat and gain in weight do well.

Laboratory Findings

Addison's disease well illustrates the maxim that the clinician should not rely on the laboratory findings for his diagnosis or prognosis. In the early stages of the disease and in chronic cases the composition of the blood may be quite normal, and a threatening relapse may be forecast more from the clinical condition of the patient than from a detailed analysis of the constituents of the blood. The laboratory findings, however, are of interest and often of use in confirming the diagnosis and the clinical concept of the degree of suprarenal insufficiency.

Blood Cells.—There is often an anaemia, but this may be masked by the increased concentration of the blood as a result of the dehydration brought about by vomiting, diarrhoea, and failure of cortical function. There may be a moderate eosinophilia and a relative lymphocytosis.

Sodium (normal: 325 mg. per 100 c.c.m. of serum).—Blood sodium is usually low, particularly in the acute cases and in crises, but it may occasionally be normal, especially in the early and chronic cases. The clinical condition is roughly parallel to the level of the blood sodium. The low blood

sodium is associated with an increased excretion of sodium in the urine.

Chlorine (normal: 350 mg. (as Cl) per 100 c.cm. of serum).—The chlorides may also be diminished, but to a less degree than the sodium.

Urea and Non-protein Nitrogen.—In crises and severe phases the urea and non-protein nitrogen are practically always high. On the other hand, the blood urea may be normal, although a crisis may be imminent. A high blood urea which continues to rise is of serious import.

Sugar.—The fasting blood sugar is frequently below normal, and there may be a further fall at a crisis. It is of little use in assessing the clinical condition, as a low blood sugar may exist with a satisfactory clinical state and normal values may be present in a crisis. However, very low blood-sugar values—for example, below 60 mg. per 100 c.cm. of blood—are of serious significance, and often occur as a terminal event. Some authorities consider that the symptoms of a relapse are due to the hypoglycaemia.

Potassium (normal: 20 mg. per 100 c.cm. of serum).—The blood potassium may be raised, especially during a relapse. A high potassium value is the most reliable chemical indication of the seriousness of the patient's condition.

Calcium (normal: 9 to 11 mg. per 100 c.cm. of serum).—Blood calcium is usually normal, but when it is raised it is of grave significance.

Serum Proteins (normal: 5.6 to 8.5 grammes per 100 c.cm. of serum).—These may be raised in a crisis when there is a decrease in blood volume due to dehydration. In the early and chronic states, when the patient is not dehydrated, they are usually normal.

Basal Metabolic Rate.—This is frequently normal, but it is often reduced, especially in a crisis, an average figure being about -18 per cent.

Gastric Juice.—Analysis usually shows hypochlorhydria or achlorhydria. X-ray examination of the suprarenals may reveal calcification in the tuberculous cases.

The most important investigations to be carried out are a determination of the serum sodium, serum potassium, and blood urea, and an x-ray examination of the suprarenals for calcification.

Diagnosis of Addison's Disease

In the diagnosis of Addison's disease other causes of pigmentation, which will not be enumerated here, must be considered. Pigmentation in the mouth is a feature of diagnostic importance. The abdominal pain may simulate abdominal conditions such as carcinoma, peptic ulcer, and renal disease, but tenderness in the loins in the tuberculous cases may be a differentiating point. One of the most important conditions to exclude is carcinoma of the alimentary tract; an x-ray examination and an examination of the faeces for occult blood are often essential, and yet carcinoma may be present although both of these investigations are negative. Pernicious anaemia and chronic nephritis with pigmentation, asthenia, and gastro-intestinal disturbances must also be excluded. Occasionally toxic goitre, especially the so-called apathetic type, with marked asthenia, mental apathy, pigmentation, low blood pressure, and little increase in basal metabolic rate may closely resemble Addison's disease. Cases of Addison's disease without pigmentation may cause considerable difficulty; in these an exacerbation of symptoms may be produced by a salt-poor diet as a diagnostic procedure, but caution must be observed as a crisis may be precipitated. Other conditions which must not be confused with Addison's disease are neurasthenia, menopausal states, essential hypotension, myasthenia gravis, and Simmonds's disease. As mentioned above, early and chronic cases may show no change in the chemical composition of the blood, but a low blood sodium, which may also occur in conditions in which there is an acidosis,

such as diabetes mellitus, high intestinal obstruction, and cholera, is a relatively constant finding.

Treatment of Addison's Disease

The treatment of Addison's disease may be considered under four headings: (1) general measures and the treatment of the underlying disease, (2) sodium therapy, (3) substitution therapy, and (4) treatment of dehydration.

GENERAL MEASURES

Rest in bed is necessary until the patients are stabilized on a maintenance dose of salt and/or cortical extract, and as they are very susceptible to cold care should be taken that they are kept warm. As they have an aversion to fats, and in view of the tendency to hypoglycaemia, the diet should be rich in carbohydrates. Because of damage to the suprarenal cortex, which is normally rich in vitamin C, it is as well to ensure that they obtain adequate amounts of this substance. Recent work suggests that a diet poor in potassium may be of considerable benefit, but details have not yet been worked out. When patients are up and about they should avoid infections, over-exertion, and exposure to cold, as any of these may bring on a relapse.

SODIUM THERAPY

In early and chronic cases it is best to start medication by the administration of salt (sodium chloride). The salt may be given in cachets or in milk in 2 to 3 gramme doses (30 to 45 grains) six times daily, the first dose being taken on waking in the morning. A disadvantage of this amount of salt is its emetic action in some patients. This may be overcome by giving sodium as a mixture of salts—for example, 6 grammes of sodium chloride, 4 of sodium bicarbonate, and 4 of sodium citrate, throughout the day. Since there is an excessive loss not only of sodium but also of chlorine in the urine, the mixture should always contain sodium chloride to prevent chlorine deficiency. The optimum therapeutic dose is variable. The result of this treatment is often a considerable improvement in the patient's condition. Appetite, strength, and weight are increased, nausea and abdominal pain are lost, but pigmentation is little if at all changed. Owing to the general metabolic improvement there may be a slight rise of blood pressure, but it does not reach the normal level. In some but not in all cases it is possible to restore the electrolyte balance of the blood to normal.

SUBSTITUTION THERAPY

The value of sodium treatment lies in the smaller requirements of cortical extract. Some patients require no extract at all; others state that they feel better when receiving extract in addition to salt; in others salt may be of no apparent value, and these will need cortical extract as well. Those who are in a crisis will certainly require extract, and it is unsafe to defer its administration in favour of salt alone: both should be given as soon as possible. In a crisis 50 c.cm. of cortical extract should be injected intravenously, and for the first week it is of advantage to continue its administration by this route (providing no reactions occur), but in successively smaller doses of 30, 20, and 10 c.cm. The daily dose necessary must be judged by the clinical condition. After the first week cortical extract may be given intramuscularly.

In cases which respond nearly all the symptoms and signs disappear. The pigmentation decreases, but it does not vanish entirely; there may be but slight change in the blood pressure. The composition of the blood tends to return to normal, with the exception of the hypoglycaemia, on which cortical extract has only a slight effect. The

basal metabolic rate is raised only if it was previously low. Results begin to be apparent in from two to four days. With improvement in the patient's health and strength the extract may be gradually reduced until the maintenance dose is reached. This varies from 1 to 5 c.cm. twice daily. In time it may be possible to stop the administration of cortical extract for some months, but this should not be attempted until the patient is gaining in weight. Treatment with sodium should not be discontinued. Progressive tuberculous lesions and secondary infections will call for increased dosage of extract.

If a crisis be protracted and in the chronic or stationary period of the disease cortical hormone exerts no striking clinical effect, and one's enthusiasm should not allow one to overlook the fact that patients have died in spite of large doses of cortical extract. Salt and cortical extract are not panaceas in the treatment of this condition.

TREATMENT OF DEHYDRATION

It is considered by many that the symptoms of a crisis are due largely to dehydration and by others to hypoglycaemia. Energetic measures should be taken to combat these conditions. In a crisis 500 c.cm. of a 5 per cent. solution of glucose in 5 or 10 per cent. saline should be injected as soon as possible intravenously and repeated if necessary during the next few days. The solution should be given slowly by the drip method, as patients in a crisis not infrequently have a rigor if it be injected more rapidly. It is essential that cortical extract be given intravenously before or during the administration of the saline, as without extract an intravenous saline is not maintained in the circulation and subcutaneous and intraperitoneal salines are not absorbed. When the vomiting is relieved fluid should be taken in large quantities by mouth.

Suprarenal Insufficiency

Acute suprarenal insufficiency is caused by acute infections, thrombosis of the suprarenal vessels, and bilateral haemorrhage into the suprarenals. Suprarenal haemorrhage may occur in the newborn as a result of eclampsia, trauma during birth, asphyxia neonatorum, and superinvolution of the cortex; in older people, as the result of severe infections, extensive burns, syphilis, and as a manifestation of a haemorrhagic diathesis.

In the newborn the clinical picture resembles pneumonia, with fever, dyspnoea, and cyanosis, but there are no pulmonary signs. In older children and adults the onset is one of acute abdominal pain, vomiting, diarrhoea, and fever. In both groups other features are: extreme asthenia and prostration, purpuric eruptions, dehydration, low blood pressure, convulsions, and coma. In the cases of haemorrhage there are, in addition, the general symptoms and signs of shock, with local signs consisting of abdominal distension and a palpable swelling in one or both renal regions. The condition is not easy to diagnose and is rapidly fatal. Therapeutic measures consist in the treatment of shock and the administration of cortical extract and of intravenous glucose salines.

Chronic suprarenal insufficiency is not well defined. Patients with debility, emaciation, hypotension, impotence, or a low basal metabolic rate are sometimes thought to be suffering from chronic suprarenal insufficiency. Some of these cases may be incomplete forms of Addison's disease, others due to hypo-adrenalism, but in the majority it is doubtful whether the suprarenals can be held responsible. No beneficial effect is obtained with cortical extract in the absence of an adrenal lesion.

[A bibliography will be given at the foot of the next article.]

TEMPORARY TREATMENT IN MENTAL HOSPITAL PRACTICE

BY

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The Mental Treatment Act of 1930, Section 5, permitting treatment of patients on a temporary basis, has now been in operation for six years. It has therefore had time to be fully investigated, and as medical officer at an institution where temporary patients constitute the largest proportion of annual admissions to any hospital in England and Wales I thought it would be of interest to survey the results and discuss the numerous difficulties.

Whether the large percentage of temporary patients is a matter for approval or not is a debatable point. Actually the number admitted to this hospital is much in excess of the general estimated figure according to even a liberal interpretation of the Act. In a memorandum published in the Board of Control Report, 1934 (Appendix, p. 88), it is pointed out that the type of patient who can be dealt with by this section of the Act is strictly limited, although it is regretted that the procedure is not being utilized in the case of rate-aided patients to anything like its full possibilities.

In Derby, however, the procedure is very much in favour, due to certain definite advantages that accrue from this method and are enumerated later. The proximity of the hospital to the town, and the fact that the public assistance authorities—officers and doctors—are familiar with the provisions of this section, are also contributory factors to the large percentage of admissions on a temporary basis. It will be noted from Table I that the percentage has risen annually, and therefore it must be a useful and desirable way of gaining admission to hospital.

TABLE I.—Showing the Annual Number of Admissions during the Past Six Years by the Three Channels of Entry, and also the Percentage Number of Direct Temporary Admissions.

Year	Voluntary	Temporary	Certified	Total	Percentage Direct Temporary Admissions
1931	8	29*	78	115	26
1932	12	34	55	101	34
1933	15	49	57	121	42
1934	27	52	56	135	39
1935	29	82	47	158	52
1936 to Nov. 30	17	58	38	113	51

The statistics published by the Board of Control show that temporary treatment is much more frequently adopted with private than with rate-aided patients, and that "one law for the rich and one for the poor" exists to some extent, though Parliament endeavoured to remedy this by the Mental Treatment Act, 1930. At the present time many non-volitional cases are not receiving the benefit of the provisions to which they are entitled, due largely to a tendency to adhere to the familiar and simpler procedure of certification. There is no doubt that the stigma attached to certification is very strong in the public mind, and that as more up-to-date accommodation is made available treatment by voluntary or temporary methods will be demanded by them and granted if it is at all applicable. It has been estimated that only one-fifth of the total number of temporary patients in England and Wales have ultimately to be certified, which indicates that this procedure is serving a useful purpose.