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TREATMENT OF ADDISON'S DISEASE

BY

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Differences of opinion still exist concerning the best method of treating patients with Addison's disease. The first real advance came with the discovery of deoxycortone acetate (D.C.A.), and early work with this substance was reported by Simpson (1938). It was soon clear, however, that D.C.A. provided only partial control. Patients remained liable to hypoglycaemic attacks, while any severe stress would still precipitate a dangerous and often fatal crisis. When cortisone became available it was evident that this substance exerted a profound effect: hypoglycaemia was abolished and the patient's improved energy, well-being, and weight gain, with improved ability to withstand stressful situations, clearly demonstrated its usefulness.

At first cortisone and D.C.A. were used together (Thorn *et al.*, 1951; MacNeal, 1951; Laurie, 1951; Fourman and Horler, 1954). Sorkin and Soffer (1953) state that D.C.A. is the most important hormonal preparation necessary in the maintenance of a patient with Addison's disease. They believe it should be employed in all cases because of its striking ability to correct disturbances in sodium and potassium metabolism. Thorn (1955) states that the amount of cortisone or hydrocortisone required to restore to normal the metabolism of sugar, etc., is too small to assure a normal electrolyte and water balance, and so he advises the addition of 10–15 g. of sodium chloride daily, or, in the majority of cases, D.C.A. with a normal sodium and potassium intake.

On the other hand, Simpson (1953) believed that when cortisone became freely available it would provide the basic treatment, supplemented, if necessary, with additional salt or D.C.A. Hart (1954) treats his adrenalectomized patients and patients with Addison's disease with cortisone alone and finds they can be maintained quite satisfactorily without D.C.A. Bishop (1955) states that cortisone has to a large extent supplanted D.C.A.

It was because of this conflict in opinion that we decided to test the effectiveness of various forms of treatment on patients with Addison's disease under their normal modes of life. In particular we were anxious to see if they could be kept in good health on cortisone alone.

Method

To determine the most suitable method of treatment, four patients with Addison's disease were studied over a prolonged period. Three of these were considered to have severe Addison's disease, while the fourth was a moderately severe case. The patients were treated for periods ranging from 9 to 21 months with D.C.A., sodium chloride, and cortisone (combined therapy), and for a period ranging from 6 to 10 months with cortisone alone. Each patient was assessed in detail before beginning treatment, when D.C.A. and salt were withdrawn, and at the end of the period with cortisone alone. As a safeguard every patient was interviewed monthly, and their blood pressure and weight were recorded.

During each of the major examinations careful attention was directed to the following factors: (1) energy and capacity for work and recreation; (2) sense of well-being, emotional tone, and mental state; (3) libido; (4) incidence and severity of infections and crises; (5) weight; (6) blood pressure; (7) pigmentation; and (8) electrolytes and blood count. Clinical details of the four patients, together with treatment adopted, are given in Table I.

Results of Treatment

Energy and Capacity for Work.—The degree of weakness and prostration suffered as a result of the illness was generally severe. In Case 1 the diagnosis had been made in 1950 and treatment with D.C.A. given. While this had restored his energy to some extent, it was apparent that he was unable to undertake all the heavy work of the farm, and required additional help from his neighbours. Owing to increasing weakness he had received a further implant of 250 mg. of D.C.A. two months before we saw him in a typical Addisonian crisis. In Cases 2 and 3 progressive weakness occurred until work became impossible. A more fluctuating weakness characterized Case 4, and for weeks at a stretch this patient was unable to do much housework; at other times she had more energy, but most household duties were a burden to her. However, before treatment with combined therapy began, she had been confined to bed for some weeks because of weakness and nausea, and was admitted to hospital for detailed investigation of her adrenal function and reserve. In these cases, with treatment the improvement in symptoms was striking, and energy returned to normal in three and nearly to normal in the other. There was no noticeable change in energy when D.C.A. and salt were stopped. The farmer (Case 1) and storeman (Case 3) both do heavy work and say they feel normal in every way on cortisone alone. One housewife (Case 2), who has a family of five to look after, is as fit and well on cortisone as on the combined treatment. The other housewife (Case 4), the only patient whose return of energy has not quite matched her original strength, felt no alteration in strength when D.C.A. and salt were withdrawn.

Sense of Well-being, Emotional Tone, and Mental State.—Three patients were mentally dull and two were depressed when untreated. All returned to normal on combined treatment, and there was no alteration in this when D.C.A. and salt were withheld.

Libido.—This was stated to be normal in one before treatment began and remained unchanged. In two, libido was depressed before treatment and improved with combined therapy. The improvement was maintained on cortisone alone. One patient had complete absence of libido following hysterectomy previously, and treatment did not alter this. Improvement in libido is likely to be related to the change in the patient's general condition rather than to any specific effect of the cortisone.

Incidence of Infections and Severity of Crises.—One patient, despite an implant of D.C.A. and additional salt therapy, was admitted to hospital in a severe crisis. One patient developed a crisis in hospital following anaesthesia for gastroscopy. A third patient had experienced recurrent

TABLE I

	Case 1 Farmer, Aged 46	Case 2 Housewife, Aged 39	Case 3 Storeman, Aged 43	Case 4 Housewife, Aged 53
Clinical features..	Known Addison's disease for 18 months; implanted elsewhere with 250 mg. D.C.A. two months before admission. Admitted in severe crisis precipitated by acute tonsillitis	Increasing pigmentation for 12 months with marked weakness. Strongly positive Kepler test. *No adrenal response to corticotrophin (17-ketosteroid output 1.2 mg./24 hrs.; following corticotrophin stimulation, 2.5 mg./24 hrs.)	3 years' loss of strength, with severe pigmentation. Addisonian crisis following gastroscopy. *No adrenal response to corticotrophin (hydrocortisone 0 mg./24 hrs.; following corticotrophin stimulation, 0 mg./24 hrs.)	12 years' history of moderate weakness, with exacerbations from time to time. More recent prostration; confined to bed before admission because of weakness and nausea, and occasional vomiting. Faintly pigmented. Kepler test strongly positive on two occasions. *No adrenal response to corticotrophin. (Urinary 17-ketosteroid output 3 mg./24 hrs.; following corticotrophin stimulation, 3.4 mg./24 hrs.)
Combined therapy and duration	Deoxycortone trimethylacetate microsuspension 50 mg. every 2 months, NaCl 4-6 g. daily, cortisone 25 mg. daily. Duration 21 months	Deoxycortone trimethylacetate microsuspension 50 mg. every 6 weeks, NaCl 6 g. daily at first, later 3 g. daily, cortisone 12.5 mg. daily. Duration 18 months	Deoxycortone trimethylacetate microsuspension 50 mg. every 2 months, NaCl 4 g. daily, cortisone 12.5 mg. daily. Duration 9 months	Deoxycortone trimethylacetate microsuspension 50 mg. every 6-8 weeks, NaCl 6 g. daily, cortisone 12.5 mg. daily for 12 months, then 25 mg. daily. Duration 14 months
Cortisone alone..	Cortisone 25 mg. daily. Duration 6 months	Cortisone 12.5 mg. daily. Duration 10 months	Cortisone 12.5 mg. daily. Duration 9 months	Cortisone 25 mg. daily. Duration 9 months

* The method adopted to test adrenal gland response to corticotrophin was the estimation of either the urinary 17-ketosteroid output or hydrocortisone output before and following adrenal stimulation by intravenous corticotrophin, 25 mg., on two successive days.

minor crises with attacks of vomiting and severe prostration. The fourth had a history of recurrent attacks of bronchitis. Since the institution of treatment no further crises and infections have occurred. It seems certain that cortisone is solely responsible for this major improvement in management.

Weight.—Combined therapy produced a gain in weight of 21 lb. (9.5 kg.) in the patient admitted in crisis (Case 1). The other three gained weight in amounts varying from 5 to 11 lb (2.3 to 5 kg.). The gain was generally maintained on cortisone alone, although slight falls were recorded in three and a gain in the fourth. The weight changes on withdrawal of D.C.A. and salt were not, however, significant.

Blood Pressure.—The effect of treatment on the blood pressure is shown in Table II. All pressures rose on combined therapy. On cortisone alone there was a slight fall in the systolic levels, but the diastolic level rose in one, remained unchanged in one, and fell slightly in two. These changes do not seem to be significant, and it is clear that a satisfactory blood-pressure level can be maintained with cortisone alone.

TABLE II.—Blood-pressure Records

	Case 1	Case 2	Case 3	Case 4
Before treatment..	95/50	120/70	110/70	125/65
Combined therapy	130/85	135/80	140/90	135/85
Cortisone alone..	120/80	125/85	135/90	130/80

These are the average B.P. levels recorded before and on combined therapy, and on cortisone alone.

Electrolyte and Blood Findings.—Blood chemistry was checked before treatment started, at the end of the period on combined therapy, and at the final assessment at the end of the period on cortisone alone. Details are noted in Table III. The values for serum sodium were a little higher than normal during combined therapy. The values on cortisone alone, however, were completely normal, and showed that, at the end of a six-months period or longer, cortisone was sufficient to maintain a satisfactory electrolyte level during the ordinary requirements of day-to-day living.

Pigmentation.—Three patients were heavily pigmented before treatment started, and one was lightly and atypically

coloured (no buccal pigment). An improvement was noted in three cases. In two of these there was definite lightening with both forms of therapy, and in one the improvement was striking. In one severely pigmented subject there was little change with either form of treatment. Because of the known failure of D.C.A. to influence pigmentation in Addison's disease it is probable that cortisone therapy is related to this improvement.

Comment

All patients were maintained in good health on cortisone alone. All say they feel as well on cortisone as they did on combined therapy; one says he feels better, as the salt tablets sickened him. Despite the relatively limited effects that cortisone has on electrolyte metabolism, it seems clear from the practical viewpoint that cortisone can maintain these patients in electrolyte balance and maintain the blood pressure at a satisfactory level.

The improvement in the patient's general well-being on cortisone is striking when compared with pre-cortisone days. The absence of crises or infection during the period under review was noticeable, and all were satisfied with their physical and mental status during treatment.

From the point of view of the patient, oral therapy with 12.5 or 25 mg. of cortisone daily is satisfactory, and the avoidance of implants or the necessity for intramuscular injections with deoxycortone trimethylacetate is an advantage.

From the experience gained in this study we believe the majority of patients with Addison's disease can be maintained in good health on cortisone alone. In certain exceptional circumstances this may not be possible, as the following example shows.

In Case 1, after the final assessment had been made, the patient noticed some weakness and nausea during vigorous haymaking in the summer of 1955. The weather was exceptionally hot and sweating was profuse, and, because of this, additional salt (6 g. daily) had to be taken. When seen by us a few days later his B.P. was 120/70 and electrolytes read: Na, 139 mEq/l.; K, 5.1 mEq/l.; Cl, 98.3 mEq/l. Therefore, in cases where sweating is profuse additional salt may be required or a compound such as 9- α -fluoro-hydrocortisone, which can be administered orally, might

TABLE III

	Case 1			Case 2			Case 3			Case 4		
	B.T.	C.T.	C.A.	B.T.	C.T.	C.A.	B.T.	C.T.	C.A.	B.T.	C.T.	C.A.
Na	129	148	146	131	154	140	141	154	140	130	151	140
K	4.5	4.2	5.1	5.1	5.5	4.6	5.7	4.6	5.9	4.5	4.6	4.9
Cl	100	101	104	99	100	103	100	102	100	101	107	104
CO ₂ C.P. ..	19	28	25	27	24	26	—	—	27	28	21	24

B.T. = Before treatment. C.T. = Combined therapy. C.A. = Cortisone alone. Figures in mEq/l.

conveniently be combined with the daily cortisone. For most of the patients in these islands, however, cortisone alone seems adequate for full health.

Summary

An account is given of a clinical trial in which four patients with Addison's disease were studied over a period of 18 to 27 months. Initial treatment with a combination of cortisone, deoxycortone trimethylacetate microsuspension, and salt for 9 to 21 months was followed by maintenance on cortisone alone for 6 to 10 months.

The effects of both forms of treatment on the clinical and biochemical aspects are detailed.

It is concluded that the majority of patients with Addison's disease can be maintained in good health on cortisone alone, without additional D.C.A. or salt.

We wish to thank Professor G. McG. Bull for his assistance in preparing this paper and for allowing us to treat one of his patients. Our thanks are also due to Dr. J. A. Smyth and Mr. D. W. Neill, who carried out the biochemical investigations.

ADDENDUM.—Cases 2, 3, and 4 have continued with cortisone alone and have been on treatment for 17, 16, and 16 months. All remain in good health and blood pressure and electrolytes are satisfactory. Case 1 is now on prednisone and D.C.A. as part of another clinical trial. Three additional cases, not described above, are being successfully maintained solely on cortisone. Treatment has been given for 10, 16, and 17 months respectively. All have regained energy, and one, a frail woman of 64, withstood the stress of a fractured tibia without undue disturbance or recourse to D.C.A. therapy. Dosage of cortisone for all cases has varied between 25 and 12.5 mg. daily. Complicating illnesses or operations will require additional cortisone, and it must be provided when necessary. Experience gained with the seven cases, during and following the trial described, has confirmed our opinion of the value of cortisone as the sole method of treatment in Addison's disease, and we now recommend it as routine treatment for new cases.

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During a tour of the slum clearance areas in Liverpool on September 28 Mr. DUNCAN SANDYS, Minister of Housing and Local Government, said that in England and Wales there were some 850,000 insanitary and sub-standard dwellings. More than a quarter of these were in the Merseyside and Manchester area, and the problem was worse in Liverpool than anywhere else. The city corporation had estimated that, of the 200,000 dwellings in Liverpool, nearly half needed to be demolished. After the war the housing shortage throughout the country made it difficult to pull down any house, however decrepit, which provided a roof over somebody's head. But now that over 2 million new houses had been built the time had come when the families in the slums should be given their fair share of these new homes. Last year in England and Wales some 75,000 people were moved out of slums into new homes. This year the number was likely to be over 100,000, and might even be as much as 120,000. The Government's target was to re-house people from the slums at a rate of 200,000 a year.

Medical Memoranda

Haemoglobin D in a Persian Girl: Presumably the First Case of Haemoglobin-D-Thalassaemia

Haemoglobin D has been found occasionally in families in North America (Itano, 1951; Sturgeon, Itano, and Bergren, 1955), in Britain (White and Beaven, 1954; Stewart and MacIver, 1956), and in Algeria (Cabannes, Sendra, and Dalaut, 1955). In Asia haemoglobin D was first found in a Sikh (Bird, Lehmann, and Maurant, 1955). It is now known that this haemoglobin variant is not rare in north-west Indians—Sikhs and Punjabi Hindus (Bird and Lehmann, 1956a, 1956b)—and in Gujeratis (Jacob, Lehmann, and Raper, 1956), in whom it was seen in 2% and 1% respectively. One family with haemoglobin D has also been discovered in the course of a survey of Turks (Aksoy and Lehmann, 1956); this has since been extended to over 400 individuals.

We have now seen haemoglobin D in a Persian girl, and, in addition to the anthropological interest of this observation, the case is noteworthy as it seems to represent the first instance of a disease hitherto not described—haemoglobin-D-thalassaemia.

CASE REPORT

A Persian girl aged 18 was seen because of vague pains and anaemia. There were no remarkable clinical findings beyond pallor. Details of the haematological investigations are given in the Table and Fig. 1. It will be seen that there

FIG. 1.—Blood smear of patient ($\times 700$). Note target cells, anisocytosis, and occasional poikilocyte.

Haematological Investigations

	Patient	Father	Aunt
Haemoglobin (g./100 ml.)	11.3	15.5	16.9
Red cells (per c.mm.)	5.41	3.92	4.71
Haematocrit (%)	35	45	46
M.C.H. (γ)	20.9	39.5	36
M.C.V. (cubic microns)	65	115	97
M.C.H.C. (%)	32.3	34.6	36.8
M.C.D. (μ)	7.16	7.86	7.24
M.C. thickness (μ)	1.6	2.4	2.4
Leucocytes (per c.mm.)	9,000	7,000	7,000
Polymorphs	5,670	4,690	5,180
Eosinophils	135	210	70
Basophils	45	—	—
Lymphocytes	2,700	1,820	1,610
Monocytes	450	280	140
Film appearance	Many target cells, Anisocytosis ++ Poikilocytosis +	Macrocytosis +	Anisocytosis +
Red cell fragility NaCl g.%	Begins 0.45 Ends 0.20	0.45 0.35	0.50 0.30
Serum bilirubin (mg./100 ml.)	0.4	0.35	0.35