DIABETES MELLITUS AND ADDISON'S DISEASE

A Discussion with Reports of Two New Cases

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TABLE 1

Type of Case	Alive at Time of Reporting	Atrophy or Fibrosis	Tuberculosis	Other Causes	Total
Simultaneous onset of Addison's disease and diabetes	Nil	5	Nil	I (haemochromatosis)	6
Diabetes preceding Addison's disease ..	3*	7	4†	Nil	14
Addison's disease preceding diabetes ..	3	I	Nil	Nil	4
Total	6	13	4	I	24

* One reported later as having died (see text).

† One had haemochromatosis also.

TABLE 2

Type of Case	Authors	Alive at Time of Report	Atrophy or Fibrosis	Tuberculosis	Other Causes	Total
Diabetes preceding Addison's disease	Adler (1947)	I				
	Baird and Munro (1954)	I				
	Balfour and Sprague (1949)—2 cases		I		I not known	
	Bickel (1945)	I				
	Breslaw (1953)	I				
	Crampton <i>et al.</i> (1949)			I		
	Heim (1940)		I			
Addison's disease preceding diabetes	Joslin <i>et al.</i> (1952)—3 cases	2		I (pre-sumed)		16
	Laqueur and Harrison (1951)		I			
	Thorn <i>et al.</i> (1951)	I				
	Ward <i>et al.</i> (1950)	I				
	Coulshed and Jones (present paper)		2			
	Gurling <i>et al.</i> (1954)	I				
	Knowlton and Kritzer (1949)		I			
Total	Soffer (1948)	I				4
	van Buchem (1950)		I			
Total		10	7	2	I	20

The combination of Addison's disease with diabetes mellitus is rare, only 43 cases having been reported in the literature from 1866 to 1955. A comprehensive review of the cases up to 1949 has been given by Simpson (1949), but a further

20 cases have been recorded since then (Tables 1 and 2). Nevertheless, the incidence would appear to be surprisingly low, in view of the well-recognized tendency of diabetics to have active tuberculous infection. Root (1934) quotes a

TABLE 3—CASE 1, J.E.G.

Date	Dietary Carbohydrate (g.)	Total Daily Insulin Requirements (units)	Blood Sugar (mg.%)
September 1946 ..	140	60	Varying from 60 to 235 mg.%
December 1946 ..	160	90	—
June 1947 ..	160	60	—
1947 to 1948 ..	160	60 to 90	Varying from 160 to 235 mg.%
1949 to 1950 ..	160	60	—
July 1951 ..	160	72	—
April 1952 ..	190	50	—
November 1952 ..	190, reducing on his own initiative to unknown amount	20	—
December 1952 ..	—	Died	—

figure of 28.4 per cent. as the actual incidence. In view of the apparent rarity of the combination, we think it justifiable to report two further cases, and to point out the difficulties in diagnosis and management.

In particular, we think it important that a search for superimposed Addison's disease be made on any diabetic who has frequent severe hypoglycaemic episodes necessitating a steady reduction in their insulin dosage, especially if this is combined with loss of weight and unexplained gastro-intestinal symptoms. Once the possibility of Addison's disease occurring in a diabetic patient is appreciated, the diagnosis should be easy, and appropriate treatment can be given without delay. This important point is clearly shown by our two cases. The diagnosis was made in the first case too late for any treatment to be effective, and the same mishap almost occurred with the second patient when we first saw him.

Case Reports

Case 1. *J.E.G., aged 36, chemical worker.*

This man was found to have diabetes during the time of his National Service, and was discharged from the Army in 1945. He was first seen by one of us (E.W.J.) in September 1946, and was admitted to hospital for observation and for attempted stabilization of his diabetes. He had no symptoms apart from slight weight loss, and routine physical examination showed nothing abnormal. His blood pressure was 135/70; chest X-ray normal; a glucose tolerance test showed a fasting blood sugar of 175 mg.%, rising steadily to 245 mg.% at 3 hours, with sugar present in all urine specimens.

He responded well to treatment, and was discharged having a 140 g. carbohydrate diet, unrestricted protein and fat, and 60 units of globin insulin daily. His diet and insulin requirements varied little during the subsequent six years (see Table 3) until April 1952, when, following a severe attack of hypoglycaemia, his diet was increased to a daily intake of 190 g. carbohydrate,

and his insulin requirements were reduced to a total of 50 units of soluble insulin per day.

He remained well on this regime until November 1952, when he began to feel vaguely unwell and complained of indigestion, nausea and anorexia. On his own initiative he progressively reduced his carbohydrate intake and his insulin dosage, until he was taking only about 120-140 g. carbohydrate per day, and 20 units of soluble insulin in divided doses. His glycosuria did not increase on this treatment.

A week before his final admission to hospital on December 24, 1952, he complained of severe lassitude, weakness and pain in his back and his legs, and of constant diarrhoea and vomiting. When he was admitted to hospital he was very drowsy, and on examination was found to have a very dry skin, with deep pigmentation of his genitalia, nipples, and buccal mucosa. His tongue was dry, but there were no palpable abnormalities in the abdomen, and no clinical abnormalities in his respiratory or central nervous systems. His temperature was normal, pulse rate 70, with a regular rhythm, B.P. 80/50, and the heart sounds were normal. There was 1.5 per cent. sugar in his urine, no ketone bodies, and normal amounts of chloride.

The clinical diagnosis of Addison's disease with diabetes mellitus was made, but before any treatment could be started the patient became rapidly worse and was dead within an hour of being admitted. Autopsy the next day (December 25) showed no abnormalities in the heart, lungs or brain. The liver was normal macroscopically, as was the pancreas, there being no obvious fibrosis or atrophy. Both suprarenals, however, were almost completely atrophied, there being no macroscopic trace of cortex whatsoever. Unfortunately, no histological sections were taken.

Case 2. *K.D., aged 23, salesman.*

This man had been known to have had diabetes since the age of 10. He was admitted to Broadgreen Hospital, Liverpool, in 1946, in hypoglycaemic coma, but responded rapidly to routine

FIGURE I

TABLE 4—BIOCHEMICAL DATA

Date	Clinical State	Blood Sugar	NPN.	K	Na	Cl as NaCl
December 1946	Stable, well	86-142 mg. %	—	—	—	—
June 1953 ..	Stable, well	120 mg. %	—	—	—	—
Oct. 20, 1953 ..	Hypoglycaemic	55 mg. %	—	—	—	—
Oct. 22-26, 1953	Frequent hypoglycaemic reactions	400-50 mg. %	—	—	—	—
Oct. 27, 1953 ..	Dehydrated, vomiting and diarrhoea	52 mg. %	96 mg. %	18.25 mg. % (4.7 m.Eq.l.)	290 mg. % (126 m.Eq.l.)	463 mg. % (79.3 m.Eq.l.)
Nov. 14, 1953 ..	Moribund, dehydrated, vomiting and diarrhoea	—	—	—	325 mg. % (141 m.Eq.l.)	—
April 1954 ..	Minor Addisonian crisis	120 mg. %	—	23 mg. % (5.9 m.Eq.l.)	—	409 mg. % (70.0 m.Eq.l.)
August 1954 ..	Well	125 mg. %	—	—	—	—
February 1955 ..	Minor Addisonian crisis	53 mg. %	—	16.5 mg. % (4.23 m.Eq.l.)	285 mg. % (123.9 m.Eq.l.)	557 mg. % (95.0 m.Eq.l.)
April 5, 1955 ..	Well	180 mg. %	—	—	—	—
May 14, 1955 ..	Ill, febrile, vomiting and diarrhoea	300 mg. %	—	—	310 mg. % (134.6 m.Eq.l.)	—
May 16, 1955 ..	No change	130-400 mg. %	—	14 mg. % (3.59 m.Eq.l.)	285 mg. % (123.9 m.Eq.l.)	—

treatment, and was discharged well, taking a 160 g. carbohydrate diet, with a total daily insulin dosage of 75 units. His subsequent diet and insulin requirements are set out in Fig. 1, and the biochemical investigations in Table 4.

In 1946, routine physical examination revealed no abnormality, B.P. 130/80, chest X-ray normal. He was kept under observation at the Broadgreen Diabetic Clinic from 1947 to 1953, and apart from one hypoglycaemic episode in 1952, he remained well, with no alteration in insulin requirements, until June 1953, when a further severe hypoglycaemic attack necessitated an increase in his carbohydrate intake to 190 g. per day, and a reduction in his total daily insulin requirements to 60 units.

He was first seen by one of us (N.C.) on October 20, 1953, in the Casualty Department of the Liverpool Royal Infirmary and admitted forthwith. He had felt the onset of hypoglycaemic symptoms at work, but, unable to obtain food quickly enough, he rapidly lost consciousness, and when seen in the Infirmary he was deeply comatose and sweating profusely, with marked hyper-tonia of all four limbs, and with bilateral extensor plantar reflexes. His blood sugar was 55 mg.%, but he recovered consciousness after he had been given 15 g. glucose intravenously, and was able to eat his supper as usual. The next morning, however, he was still very drowsy, despite having had no more insulin, and his blood sugar was 45 mg.%. Physical examination at this stage revealed nothing abnormal in his chest or abdomen, and all his reflexes were now normal. The blood pressure was 100/55 and the heart sounds normal. There was an established diabetic cataract on the left, and a well-marked diabetic retinopathy on the right. Chest X-ray was normal, as was the E.C.G.

Anorexia prevented him from taking his full diet, and he again began to show symptoms of hypoglycaemia, necessitating a rapid reduction in his total daily insulin, from 60 to 20 units, over the next four days. A curious feature noted at this stage was an alarming fluctuation of blood sugar levels from hour to hour, bearing no apparent relationship to the times of his insulin injections, and with hypoglycaemic symptoms appearing when the blood sugar level was as high as 100 mg.%. The hypoglycaemic reactions continued despite the marked reduction of insulin dosage, and in view of his increasing anorexia the insulin had to be discontinued completely. Two days later, however, he was very much worse, the anorexia having progressed to constant vomiting of everything taken by mouth; he was drowsy and apathetic, and clearly dehydrated.

Complete reappraisal at this stage (October 27)

revealed no evidence of ketosis. His B.P. had fallen to 80/55, and for the first time pigmentation was noted on his buccal mucosa. The areolae were very dark, and several pigmented moles on his arms had become almost black. No new features were found in the respiratory, alimentary or central nervous systems. X-rays of his abdomen, both at this stage and later, showed no evidence of suprarenal calcification. The relevant biochemical investigations are shown in Table 4.

It now seemed clear that he was suffering from Addison's disease, and treatment was started with intravenous glucose-saline, intramuscular DCA (11-desoxycorticosterone acetate) and intravenous whole suprarenal extract given as 'Eschatin' (Parke Davis). Cortisone was not given because of the possibility of precipitating an uncontrollable diabetic ketosis. Very small doses of insulin were given at 4-hourly intervals dependent upon the blood and urine sugar levels. His general condition rapidly improved, the B.P. rose to 115/60 and the serum electrolytes returned to normal. At this stage, injection of 25 mg. ACTH produced no significant fall in the number of circulatory eosinophils; his urinary ketosteroids were found to be 1.6 mg./24 hours, and an insulin tolerance test produced a fall from 300 to 100 mg.% in the blood sugar, half an hour after 1.5 units of soluble insulin had been given intravenously.

He remained well, now taking 180 g. carbohydrate diet, and 20 units of insulin daily, until shortly after his DCA injections had been replaced by an implant on November 14. He then contracted acute follicular tonsillitis, and within 6 hours of the onset of the fever he had entered into a very severe Addisonian crisis, the diarrhoea amounting to continuous faecal incontinence, and it was accompanied by uncontrollable vomiting. Within 2 hours of the onset of the diarrhoea he had become grossly dehydrated and appeared moribund. The B.P. was 75/40, although the serum electrolytes were normal. It required the rapid intravenous infusion of 5 pints of 5 per cent. glucose saline in 2 hours to save his life, but within 2 days he was well again, although still showing a very marked insulin sensitivity. His B.P. had risen only to 105/65, and it seemed likely that the DCA implant was not being absorbed. Accordingly, it was supplemented with depot injections of a microcrystalline suspension of DCA, given as 'percorten crystules' (Ciba) 100 mg. every 4 weeks. This proved entirely satisfactory, and was continued until the patient died. At this juncture cortisone was introduced into the treatment, beginning with 2.5 mg. b.d., gradually increasing to 5 mg. b.d. This tentative

treatment produced no rise in insulin requirements, but his general condition continued to improve, and he was discharged from hospital. A further attack of tonsillitis in April 1954 precipitated a mild Addisonian crisis, and he was readmitted to the Royal Infirmary. Increased cortisone, given as 10 mg., t.d.s. failed to control the crisis, but the appearance of ketone bodies in the urine prevented an increase in dosage, and it was necessary to give parenteral 5 per cent. glucose saline, 'Eschatin,' and DCA injections to bring him back to normal. The cortisone dosage was maintained at 25 mg. daily, his diet was increased to 200 g. carbohydrate per day, and his insulin requirements rose to 60 units per day coincident with the increase in cortisone. He remained well on this regime until May 1955, apart from a minor Addisonian crisis in February 1955. On May 13, 1955, he noted a slight sore throat, which was very much worse the next day, and it was accompanied again by vomiting and diarrhoea, necessitating his readmission to the Royal Infirmary, on this occasion for the last time. Examination revealed a temperature of 101°F., B.P. 110/80, clear lung fields, and no palpable abnormalities in the abdomen. His tonsils and fauces were covered by a greyish-white exudate, which on culture grew only monilia albicans. The same organism was later recovered from his sputum and faeces.

The biochemical findings are shown in Table 4, and in spite of the high blood sugar, he was again treated as having an acute Addisonian crisis by the measures utilized on previous occasions. Penicillin and later oxytetracycline failed to influence the fever, the exudate on his fauces became more extensive and he had severe dysphagia, attempts at swallowing being followed by uncontrollable coughing and vomiting. The diarrhoea persisted also. His general condition steadily deteriorated and he died on May 23.

Autopsy was performed by Professor H. S. Sheehan, one hour after the patient died. Externally, there was a noticeable absence of generalised pigmentation, and in particular the perineum, genitalia, axillae and nipples were normal. No abnormal pigmentation of the buccal mucosa was found, there was normal distribution and development of body hair, and the external genitalia were normal. Macroscopic and histological examinations of the brain, cerebral vessels, thyroid, parathyroid, great vessels, thymus, bladder, prostate, and testes were normal. The liver margin projected 10 cm. beyond the costal margin, but otherwise the organ was normal.

The spleen tip extended to the left costal margin, and the whole organ weighed 400 g., but the sections were normal. Likewise there was a

generalized lymph gland enlargement, but general and histological examination was otherwise normal.

The heart weighed 400 g. and was of normal development. One segment of the left main coronary artery showed a severe degree of atheromatous change, and a few petechiae could be seen beneath the left ventricular endocardium.

Both lungs showed slight oedema, but there was no evidence of old or recent tuberculous infection. Sections examined showed the presence of numerous 'heart failure' cells. The right pleural cavity contained 500 c.c. of turbid yellow fluid, with fibrinous exudate covering the right lower lobe. Culture specimens of the fluid were not taken.

The kidneys presented a normal gross appearance, but histologically about 5 per cent. of the glomeruli were completely fibrosed, and all the others showed reduction in the capillary loops, often with deposits of hyaline in capsular epithelium, and occasionally with the appearance of an early Kimmelstiel-Wilson lesion.

The pituitary appeared normal macroscopically, and the only prominent feature histologically was an increase in the number of basophil cells at the expense of the chromophobes.

The pancreas was normal to the naked eye and weighed 80 g. Histological examination showed very few islets, but the islet cells themselves appeared normal, there being no hyalinization or hydropic change. Attempts to demonstrate the alpha and beta cells by special stains were unsuccessful. The small arteries and arterioles of the pancreas, as elsewhere, showed hyaline thickening of the intima and internal elastic lamina.

The suprarenals each weighed 1.3 g., this weight including a good deal of perirenal fat. The glands were of normal extent, and showed no fibrosis, caseation, or capsular thickening. The cortex everywhere was seen as a narrow layer of grey translucent tissue, with no lipoid appearance. The medulla was a translucent yellow colour. Histology showed that the cortex had been completely replaced by fibrous tissue. There was numerous foci of lymphocytes throughout the medulla, but otherwise this part of the gland was normal.

Discussion

Much experimental work has been done in recent years on carbohydrate metabolism; the site and action of insulin, and the numerous inter-relationships between pancreatic islets and the other endocrine glands. Several discrepancies in the results of animal experiments have been found, but it should not be forgotten that there is a state of constant dynamic equilibrium in the functioning of the intact animal, and that separate

consideration of individual hormones may give a quite artificial picture of actual processes involved. In addition to this, mechanism of action may differ in unrelated animals and in man.

Much of this recent work has been reviewed by Marble, in Joslin's 'Treatment of Diabetes Mellitus' (1952), and will not be reiterated here. However, it seems certain that the influence of insulin on carbohydrate metabolism is mediated mainly through facilitation of the hexokinase reaction in the phosphorylation of glucose to glucose-6-phosphate. The anterior pituitary, directly through the growth hormone, and indirectly by the suprarenal cortex, inhibits this reaction, and insulin acts as an antagonist to both these hormones. Thus when insulin deficiency occurs, several things happen. There is decreased rate of utilization of glucose in muscle, the rate approaching normal only at high concentrations of glucose. There is increased breakdown of liver glycogen to glucose and increased gluconeogenesis from protein and probably from fat. Glycogen formation from glucose is greatly reduced in liver and muscle, though it does not completely cease. These facts are shown clinically by the decreased carbohydrate tolerance, the hyperglycaemia and glycosuria. Ketonæmia and ketonuria occur because of derangement in the metabolism of fat and protein, but the exact mechanism is not clear.

In Addison's disease the principal defect in carbohydrate metabolism is the inability to obtain glucose in sufficient quantities from both endogenous and exogenous sources, to counteract the increased utilization caused by the unopposed action of insulin. There is decreased conversion of protein to glucose, and a decreased rate of glucose absorption from the gut because of the mineralocorticoid deficiency. The liver glycogen stores are depleted, but muscle glycogen is not diminished. Clinically, these features are shown as an extreme insulin hypersensitivity, with abnormally low blood sugar levels during fasting, either experimentally or in the anorexia and vomiting associated with Addisonian crisis. Hypoglycaemic reactions may occur, often at higher blood sugar levels than usual. The glucose tolerance test shows a flat curve, but if the glucose is given intravenously there is a normal rise in the blood sugar followed by a rapid fall to hypoglycaemic levels when the insulin secreted as a result of the stimulus of the rising blood sugar begins to take effect.

Protein metabolism is affected as conversion to glucose is lessened, and fat metabolism is also affected, in that there is decreased formation of ketone bodies, but the exact mechanism is not known.

Addison's disease and diabetes mellitus, therefore, in many ways affect metabolism in diametrically opposite fashion, and when they occur together there is considerable modification of the abnormal metabolism caused by each. Thus gluconeogenesis in the liver is lessened because of the lack of glucocorticoids, but the liver glycogen stores do not fall as far as would be expected, since glucose utilization is increased, and the effective blood sugar level falls. Clinically, when Addison's disease develops in a diabetic patient, these facts are shown as a fall in the blood sugar levels, with diminution of glycosuria and progressive decrease in insulin requirement. The lack of cortical hormones causes increased insulin sensitivity, with wide fluctuations of blood sugar levels, and hypoglycaemic reactions occurring with comparatively high blood sugars. If ketosis occurs when Addison's disease is present, the severity is much less, because of the modification of the protein and fat metabolism.

The above features have been pointed out by Simpson (1949, 1950, 1953), Balfour and Sprague (1949), Thorn *et al.* (1951) and Crampton *et al.* (1949), though the latter point out that the increased carbohydrate tolerance and insulin sensitivity may also occur in hypopituitarism, hypothyroidism, liver disease, and congestive cardiac failure. However, Ward *et al.* (1950) have reported a patient with diabetes mellitus and Addison's disease in whom there was no decrease in the requirements of insulin and no insulin hypersensitivity. They suggested that these features were absent because of only partial adrenal failure. When Addison's disease supervenes on a previous diabetic state, there is often loss of weight despite adequate diabetic control, and in the absence of the more common complications of diabetes such as pulmonary tuberculosis, evidence of Addison's disease should be looked for.

With regard to the laboratory investigations which may be carried out, Simpson (1949) has observed that the Kepler test is not necessarily valid in the presence of diabetes, especially if the diabetes is not well controlled, and it was because of this, and the patient's precarious state, that the test was not done in Case 2. Simpson also states that if the diabetes is severe, the patient's sensitivity to small intravenous doses of insulin may not be manifest at the time of the test, although this was not so in our Case 2.

Both our cases developed Addison's disease where diabetes mellitus was established, and in each case the cause of the Addison's disease was atrophy of the suprarenal cortex.

Case 1 showed mainly the progressive decrease in insulin requirements (Table 3) associated with

anorexia and vomiting, occurring very quickly over a period of four weeks. The clinical diagnosis of Addison's disease seemed clear, but was made too late to save the patient's life, and consequently no investigations could be undertaken.

Case 2 also showed progressive reduction in insulin requirements (Fig. 1), beginning in June, 1953, and associated with frequent hypoglycaemic reactions. The more rapid reduction of insulin requirements occurred in October 1953, with the onset of acute Addisonian symptoms, and he remained insulin sensitive until adequate cortisone replacement therapy was given, when his insulin requirements rose again to the same level as before the onset of the acute Addisonian symptoms. He also showed other characteristic features, especially the prolonged hypoglycaemic attacks which proved very resistant to treatment, and occurred at relatively high blood sugar levels. Although several episodes of vomiting and diarrhoea occurred, he developed no ketosis until he was given cortisone, but there was never any significant weight loss.

Pathology

The two common causes of Addison's disease are bilateral tuberculous destruction of the suprarenals, and idiopathic atrophy or fibrosis. It has been pointed out that Addison's disease in diabetes is rare, but what is even more curious is the fact that atrophy appears to be a much commoner cause than tuberculosis. Simpson (1949) reviewed 24 cases, including two new cases of his own, the whole being summarized in Table 1. Three of the cases developing Addison's disease after the diabetes were still alive at the time Simpson wrote his review, but the case occurring after denervation of the suprarenals is quoted in Joslin's textbook on the treatment of diabetes mellitus (1952) as having died.

Twenty-one further cases have been recorded, including the two in this paper, and are summarized in Table 2. Only 20 cases are shown in the table, the remaining case reported by Sprague *et al.* (1947) had 'both diseases in relatively mild form,' but no details are given. Two other cases in the same paper appear to be the same as those reported by Balfour and Sprague (1949).

As will be seen from Tables 1 and 2, atrophy is more than three times commoner than tuberculosis as a cause for the suprarenal pathology shown at autopsy, the exact figures being 20 cases of atrophy or fibrosis and 6 tuberculous. Seventeen patients were still alive when reported in the literature, hence the aetiology of their Addison's disease is not proven, though none showed calcification of the suprarenals on X-ray, or had tuberculosis, so that atrophy or fibrosis seem the

most likely cause in these patients also. Why there should be this great predominance of atrophy or fibrosis is not known, nor is it clear whether there is any common aetiological factor for the diabetes mellitus and the Addison's disease.

Treatment

As will be readily appreciated, replacement therapy for two simultaneously occurring and apparently incompatible conditions, is difficult in the extreme. Before cortisone became available, the insulin hypersensitivity was the main difficulty, and hypoglycaemic coma was a common cause of death. With this in mind, it is preferable to use soluble insulin rather than any of the long-acting preparations since any hypoglycaemia which may occur will be more easily controlled. Diet should be regulated with a high carbohydrate intake, because of the insulin hypersensitivity and the impaired gluconeogenesis in Addison's disease.

We believe that DCA (11-desoxycorticosterone acetate) is also necessary, in one or other of its preparations, although it should be used in conjunction with cortisone. Some authors have thought that DCA alone increases insulin sensitivity (Crampton *et al.* (1949), Loeb (1947), Bloomfield (1939), Bickel (1945)), but these experiences are in contrast with more general experience and with theory. Van Buchem (1950), moreover, found that carbohydrate tolerance was less when his patient was treated with DCA. We found no apparent change in carbohydrate tolerance when DCA was given alone, and we found the microcrystalline suspension of 'percorten crystals' injected monthly, a very satisfactory method of administration.

Cortisone (11-dehydro-17-hydroxycorticosterone-21-acetate) has revolutionized the treatment of all cases of Addison's disease, and when diabetes mellitus is not present, is certainly the treatment of choice, both routinely and in crisis. When diabetes is also present, however, it should be used with the greatest care, because of the danger of precipitating uncontrollable diabetic ketosis. Ingle, quoted in the *British Medical Journal* (1950), produced diabetes in rats with injections of cortisone, the diabetes being incapable of control by insulin even in doses of up to 1,000 units per day, indicating the diabetogenic properties of the drug. Our second case remained well on 25 mg. of cortisone per day, but increase to 30 mg. per day in the treatment of Addisonian crisis was followed by the appearance of ketone bodies in the urine, and the dosage had to be reduced. Balfour and Sprague (1949) reported cases where ketosis was precipitated by 4 mg. cortisone every 6 hours, and both Baird and Munro (1954), and Simpson (1953)

have reported the rapid onset of ketosis when a dosage of 25 mg. per day was given.

It is clear, therefore, that cortisone must be introduced slowly and cautiously, but if this is done, the diabetic condition becomes much more stable and easily regulated. There is loss of insulin hypersensitivity, with less fluctuation of the blood sugar level, and less tendency to hypoglycaemia, despite the necessary increase of insulin dosage. We suggest that the dosage of cortisone be started as 2.5 mg. twice daily, slowly increasing to 25 mg. daily, with coincident adjustment of the insulin given. Throughout this period of increasing cortisone dosage, a strict watch must be kept for the presence of ketone bodies in the urine. If they appear, the cortisone must be reduced in amount when even so slight a reduction as 5 mg. per day may be sufficient to abolish the ketosis, as occurred in our Case 2.

Because of the difficulties coincident to the use of cortisone in the treatment of the Addisonian crisis, we found it necessary to use intravenous whole suprarenal extract, in the usual doses, and had no trouble with developing ketosis, despite adequate control of the crisis.

Summary

Two new cases of the rare combination of Addison's disease and diabetes mellitus are reported. The previous literature has been briefly reviewed, with the physiology, pathology and clinical picture. Treatment of the patients is discussed, with emphasis on the use of cortisone, its advantages and drawbacks.

It is suggested that the development in any case of diabetes mellitus of progressive reduction in insulin requirements; frequent and severe hypoglycaemic reactions; a steady weight loss, and unexplained gastro-intestinal symptoms, should

promote a diligent search for superimposed Addison's disease.

We are indebted to Dr. C. A. Clarke for allowing us to have access to his records of Case 2 during the time when the patient was under supervision at Broadgreen Hospital, Liverpool; to Professor H. L. Sheehan of the Department of Pathology, University of Liverpool, for his autopsy report on Case 2, and to Drs. F. D. Kitchen and M. K. Alexander for their help in the management of the same case.

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