INSULIN RESISTANCE IN HAEMOCHROMATOSIS

JAMES BUCHANAN,

M.B., M.R.C.P., (Edin), M.R.C.P., (Glas).

E. T. YOUNG,

M.B.,[†]M.R.C.P., (Edin), M.R.C.P., (Glas),
M.R.C.P., (Lond).*From the Department of Metabolic Research, Victoria Infirmary, Glasgow*

ROOT (1929) gave theoretical reasons for regarding insulin resistance as present when a patient requires more than 200 units of insulin daily. This figure was derived from the insulin requirements of depancreatized animals but has been accepted as a satisfactory and practical although clearly arbitrary standard (Martin, Martin, Lyster and Strouse, 1941; Davidson and Eddleman, 1950; Oakley, Field, Sowton, Rigby and Cunliffe, 1959). Defined in this way, insulin resistance has been described rarely in haemochromatosis. Hitherto only 11 cases have been recorded (Root, 1929; Allan and Constam, 1929; Engel, 1934; Eskin, Franklin and Lowell, 1953; Stauffer, Butt and Dockerty 1954; Colwell and Weiger, 1956; Uhry, Marcel and Cohen, 1957; Justin-Besancon, Pequignot, Deuil, Etienne, Magdelaine and Jullien, 1960; Michon, Larcen, Huriet and Vert, 1961; Heath, 1965). The doses of insulin required are shown in Table 1.

This report gives details of two additional cases.

Case No. 1.

In June 1954 when he was aged 50 years, this patient was found to have diabetes mellitus. His liver was palpable 4 cm. below the costal margin but no other abnormalities were found on physical examination. The diabetes was stabilised with 80 units of IZS lente daily. Because of midday glycosuria the proportion of IZS amorphous was increased but without significant benefit.

In October 1964 diabetic control became frankly poor and he required admission to hospital. He looked ill and had clearly lost weight. His skin showed widespread slate-grey pigmentation. The liver edge was now 10 cm. below the costal margin.

Investigations: The serum iron was 232 µg./100 ml. The serum bilirubin was 0.7 mg./100 ml. and the alkaline phosphatase 14.7 King-Armstrong units. Thymol turbidity was 2 units. The serum proteins totalled 7.7 g./100 ml. of which albumin was 4.2 g. and globulins 3.5 g./100 ml. Liver biopsy showed diffuse haemosiderin deposits in the parenchymal cells and portal tracts, in keeping with haemochromatosis. The urine contained ketone bodies and 2% glucose. The blood sugar was 348 mg./100 ml.

Treatment: with three doses of soluble insulin daily was begun. Four days after admission, i.e. on 24th October, ketonuria disappeared and did not recur. The insulin requirement increased rapidly and reached a maximum of 864 units daily on 6th November. He had two mild hypoglycaemic reactions and from 11th November the dose was stabilised at 624 units daily. The degree of glycosuria varied and blood sugar levels fluctuated between 109 and 360 mg./100 ml. He left hospital on 26th November, still taking 624 units of soluble insulin daily. In March 1955 the insulin requirement began to fall but exceeded 200 units daily until the latter part of August 1955. Insulin resistance had thus persisted for approximately nine months.

Progress: During the next three years the dose of insulin was decreased gradually. By 1958 satisfactory control was maintained with 48 units of soluble insulin daily. Treatment of haemochromatosis by repeated venesection was then started and by March 1963 98 pints of blood were removed. The daily insulin requirement fell to 36 units soon after this treatment was begun and remained constant until shortly before his death. In February 1963 he developed a large tender mass in the left hypochondrium with ascites and oedema. Biopsy revealed a hepatoma. There was no change in his insulin requirement until the terminal phase when he was given 20 units daily. He died on 19th August 1963.

TABLE 1

PREVIOUSLY REPORTED CASES OF HAEMOCHROMATOSIS WITH INSULIN RESISTANCE

Authors	Maximum daily dose of insulin (units)
1. Root, 1929	1,080
2. Allan and Constam, 1929	1,000
3. Engel, 1934	1,365
4. Eskin et al., 1953	1,050
5. Stauffer et al., 1954	330
6. Stauffer et al., 1954	450
7. Colwell and Weiger, 1956	11,400
8. Uhry et al., 1957	7,300
9. Justin-Besancon et al., 1960	500
10. Michon et al., 1961	260
11. Heath, 1965	384

TABLE 2

CASE 2. PERIOD OF PREDNISOLONE THERAPY, SHOWING BLOOD SUGAR LEVELS AT 11 A.M. AND 3 P.M., DAILY INSULIN REQUIREMENT AND DOSE OF PREDNISOLONE.

Date	Blood sugar (mg./100 ml.)		Daily Insulin (units)	Dose of Prednisolone
	11 a.m.	3 p.m.		
25 November	272	—	204	—
26 November	—	—	204	—
27 November	210	216	204	10 mg. t.i.d.
28 November	243	259	204	10 mg. t.i.d.
29 November	340	350	280	5 mg. t.i.d.
30 November	192	184	204	5 mg. t.i.d.
1 December	173	227	204	2.5 mg. t.i.d.
2 December	250	—	204	—
3 December	—	—	184	—

Necropsy: The liver weighed 1695 g. and showed an overall picture of fine cirrhosis. In addition, numerous white nodules of apparently neoplastic tissue were scattered throughout the substance of the liver, mainly in the left lobe. Microscopic examination of the liver sections showed established portal cirrhosis and haemochromatosis. The neoplastic tissue consisted of primary hepatoma.

Case No. 2.

This patient was found to have diabetes mellitus in May 1960, when he was aged 65 years. Control was achieved initially with IZS lente 32 units daily but within a month chlorpropamide, 250 mg. daily was substituted. Control remained excellent. In March 1961 it was noted that his skin was pigmented. The liver was not palpable but it was thought he might have haemochromatosis. The serum iron was 235 µg./100 ml. and the serum iron binding capacity 323 µg./100 ml., i.e. 72.8 per cent saturation.

Subsequently diabetic control became poor during respiratory infection. IZS lente, 32 units daily, was resumed and proved effective until October 1961. He was then admitted to hospital for stabilisation. There was widespread brownish skin pigmentation and the liver was markedly enlarged. Liver biopsy gave evidence of haemochromatosis but skin biopsy was negative.

Treatment: He required two or three injections of soluble insulin daily. Ketonuria was eliminated quickly. During the 17 days from 25th October until 11th November he was given more than 200 units of insulin daily, reaching a maximum dose of 320 units on 27th October and again on 6th November. There was variable glycosuria and the blood sugar fluctuated between 78 and 315 mg./100 ml. After a temporary decrease to 132 units daily, a second phase of insulin resistance began on 25th November and lasted for eight days, during which the maximum dose was 280 units daily.

It was thought that the patient might have developed antibodies to exogenous insulin and thus have incurred insulin resistance. An attempt was made to demonstrate this by the passive cutaneous anaphylaxis test (Oakley and colleagues 1959) but the result was negative. In an endeavour to reduce the insulin requirement prednisolone was given from 27th November until 1st December. The duration of corticosteroid therapy was too short for its effect to be assessed fully but the increased blood sugar levels on 29th November led to its withdrawal. (Table 2).

Progress: Treatment of the haemochromatosis by repeated venesection was begun shortly before the patient left hospital on 4th December 1961. During the next four years 20 pints of blood were removed. The size of the liver decreased and skin pigmentation faded slowly. There was a gradual but progressive fall

in the daily insulin requirement from 184 units in December 1961 to 44 units in the early part of 1966.

Discussion

Diagnosis of Haemochromatosis

The diagnosis of haemochromatosis in both cases was confirmed by liver biopsy. The importance of this procedure was emphasised by Finch and Finch (1955) who stated that the degree of skin pigmentation is quite variable. Significant deposits of haemosiderin may not appear in the skin until late in the course of the disease. On this account and also because much of the pigmentation may be due to an increase in the melanin content of the skin, biopsy of even markedly pigmented skin may be negative. Thus skin biopsy may be negative when liver biopsy yields positive findings (Stauffer and colleagues, 1954) as in Case 2 of the present report.

Insulin Requirements

Finch and Finch (1955) stated that about 82 per cent of all patients with idiopathic haemochromatosis develop diabetes mellitus and 72 per cent require insulin, the average daily dose being 54 units. Earlier reports such as that of Sheldon (1934) suggested that diabetes associated with haemochromatosis was of severe type and difficult to control. Subsequent observations have not supported this view. King and Downie (1947) stated that in no instance did they encounter difficulty in controlling the diabetic state. Davidson and Eddleman (1950) and Loneragan and Robbins (1959) considered that most patients with haemochromatosis responded to insulin as did any other patients with diabetes mellitus and added that some patients were unduly sensitive. Except for the large daily doses required during the periods of insulin resistance the amounts of insulin taken by the patients described in this report were unremarkable, namely 36 and 44 units respectively.

Use of Sulphonylureas in Haemochromatosis

In Case 2 of the present report the use of chlorpropamide, 250 mg. daily, achieved excellent control throughout a period of nine months. During this

period cutaneous pigmentation was noted and the serum iron level and saturation of iron binding capacity were in keeping with haemochromatosis. Although that diagnosis was not then proved by liver biopsy, it seems most likely that the patient had haemochromatosis from the onset of his symptoms. It has been postulated by Creutzfeld and Soling (1961) that some response to sulphonylurea drugs may occur in mild cases before the pancreatic islet cells are totally destroyed. The effect may be similar to that occurring in alloxan diabetes when some insulin is still produced. Creutzfeld and Soling (1961) reviewed several reports of the use of sulphonylurea drugs in the treatment of haemochromatosis, either alone or in combination with insulin and concluded that they were ineffective. An additional report by Uhry and colleagues (1957) described a patient in whom the use of carbutamide was accompanied by the rapid cessation of glycosuria but when the drug was stopped because of mental depression control remained good for two months. It is therefore difficult to assess the part that the sulphonylurea played in controlling the diabetic state and it is of further interest that when glycosuria did recur tolbutamide failed to produce satisfactory control. Chlorpropamide was used in one case by Choudhury and Ganguly (1962) but during the third week of treatment insulin was added to the regime and one must therefore presume that the sulphonylurea proved ineffective. Seftel, Keeley, Isaacson and Bothwell (1961) cited the case of a male Bantu whose diabetes was stabilised at first with 120 units of insulin daily but whose requirement fell until tolbutamide was substituted for insulin. No other details of the case were given.

Effect of Venesection on Insulin Dose

It was suggested by Davis and Arrowsmith (1952, 1953) that venesection might improve the carbohydrate metabolism in haemochromatosis. They reported decreased insulin requirement in one case after massive venesection. A similar case was described in Myerson and Carroll (1955). Reduction in insulin requirement was reported by McAllen, Coghill and Lubran (1957) in one of two cases. Only one of four cases recorded by Brody, McKenzie and Kimball (1962) had a reduction in insulin dose but it was considered that better control was achieved on the other three patients after venesection. Peskoe and Siegel (1962) reported one case with no change of insulin dose. Thus carbohydrate metabolism and insulin requirement do not respond uniformly to treatment of haemochromatosis by repeated venesection.

There was no significant alteration in the amount of insulin required by Case 1 during the period of

repeated venesection. In all 98 pints of blood were withdrawn over a period of 4½ years. There was an early fall in the patient's daily insulin dose from 48 to 36 units followed by more than four years during which no change occurred. The disappearance of insulin resistance in this case was unrelated to venesection. In Case 2 venesection was begun at the time insulin resistance ended. During the next four years there was a gradual fall in the patient's insulin requirement from 184 units to 44 units daily. It is by no means clear, however, that these events were cause and effect.

Insulin Resistance

Insulin resistance is rare in haemochromatosis in the absence of ketosis or other predisposing factors. It may be due to a number of different insulin antagonists, some of which have the properties of antibodies. Oakley and colleagues (1959) suggested the use of passive cutaneous anaphylaxis in the guinea-pig to demonstrate the presence of antibodies and reported that prednisone abolished insulin resistance in patients who had a positive test but failed to do so when the test was negative. The attempt to demonstrate antibodies in Case 2 gave a negative result.

The underlying cause of the insulin resistance was not demonstrated in either of the cases described in this report. In neither case was resistance associated with diabetic ketoacidosis or any inter-current illness or infection that might have predisposed to an increase in insulin requirement. Only 51 cases of insulin resistance had been reported by 1950 (Davidson and Eddleman, 1950) and of these, three cases (6 per cent) had haemochromatosis (Roor, 1929; Allan and Constam, 1929; Engel, 1934). Haemochromatosis occurs in only about 0.4 per cent of diabetics (Boulin and Urry, 1949; Marble and Bailey, 1951; Bell, 1955). Thus insulin resistance is probably more common in cases of haemochromatosis than in the diabetic population as a whole.

Olsen and Nuetzel (1950) found that hepatic disease was associated with a form of insulin resistance. Further, of six cases of insulin resistance treated with prednisone by Oakley and colleagues (1959) three had apparent liver disease. Possibly the insulin resistance that occasionally occurs in association with haemochromatosis is related to the hepatic lesion. An investigation of insulin antagonism in haemochromatosis, even in the absence of overt insulin resistance, might be profitable.

Summary

Insulin resistance with a daily requirement of more than 200 units in the absence of ketosis or other predisposing factors is rare in haemochro-

matosis. Only eleven cases have been recorded hitherto. Two additional cases are now reported.

The first (male, 50 years) was treated initially with 80 units of IZS lente daily. Control was good for two months but he then developed resistance and required up to 864 units of soluble insulin daily. After nine months his requirement fell rapidly and was eventually 48 units daily. Regular venesection was then begun, and the requirement fell to 36 units daily. Nine years from first diagnosis he died from hepatoma.

The second (male, 65 years) was at first well controlled with chlorpropamide. Later he required insulin and developed resistance. This persisted for more than two weeks during which he required up to 320 units of soluble insulin daily. Subsequently repeated venesection was performed over a period of four years. The insulin requirement fell to 44 units daily.

No satisfactory explanation is apparent for the temporary insulin resistance in these cases but a further study of insulin antagonism in haemochromatosis seems desirable.

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