

From the Nottingham General Hospital, Nottingham, Great Britain.

## SOME CLINICAL ASPECTS OF INSULIN ANTAGONISM<sup>1</sup>

By

MICHAEL WELLS

By a remarkable accident in 1889 von *Mering* and *Minkowski* discovered that diabetes could be induced in a dog by removing the pancreas. *Opie*'s observation in 1901 that the Islets of Langerhans were sometimes abnormal in diabetes paved the way for *de Meyer* and later *Sharpey-Schafer* to forecast confidently and accurately, as it transpired, the existence of a hormone which was named "insuline". No better name could have been chosen for the substance subsequently isolated by *Banting* and *Best* in 1921.

It soon became clear, however, that other endocrine glands secreted substances which antagonised the effects of insulin. *Houssay* and his colleagues in 1937 alleviated experimental diabetes in dogs by hypophysectomy and Long and Lukens in 1936 produced similar, though less dramatic results, by adrenalectomy. In partially depancreatized dogs an excess of thyroid hormone will produce glycosuria. (*Houssay*, 1942).

Total pancreatectomy in man has shown that only 40 units or so of insulin are required to control the resulting diabetes (*Goldner & Clark* 1944). Many diabetics, however, need daily doses far greater than this and in such instances absolute insulin lack cannot be an adequate explanation. The discovery of endocrine and non-endocrine antagonists over the past 41 years has helped to build up piece by piece this most complex of metabolic puzzles which we now cautiously refer to as the

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diabetic "syndrome". Table 1 lists the factors which may contribute to or cause a state of diabetes and emphasises the complexity of the problem.

TABLE I  
*Diabetogenic factors (modified from Williams, R.H.).*

| <i>Dietary</i>                                           | <i>Beta-cell destruction or removal.</i>                         |
|----------------------------------------------------------|------------------------------------------------------------------|
| (A) High caloric intake for frequent and long intervals. | (A) Pancreatectomy.                                              |
| (B) Starvation.                                          | (B) Chemicals - Alloxan, dehydroascorbate and many others.       |
|                                                          | (C) Pancreatitis.                                                |
|                                                          | (D) Neoplasm.                                                    |
| <i>Hormonal</i>                                          | <i>Other.</i>                                                    |
| (A) Growth hormone.                                      | (A) End organ refractoriness to insulin (genetic).               |
| (B) Prolactin.                                           | (B) Insulin antibodies or other antagonists.                     |
| (C) A.C.T.H. and glucocorticoids.                        | (C) Genetic abnormalities in insulin synthesis and/or secretion. |
| (D) Glucagon.                                            | (D) Liver disease.                                               |
| (E) Adrenalin.                                           |                                                                  |
| (F) Pitressin.                                           |                                                                  |
| (G) Oestrogen.                                           |                                                                  |

Epinephrin, glucocorticoids and growth hormone are the most important of the so called physiological insulin antagonists, (see *de Bodo* and *Altszuler* 1958 for full review), not only because they exacerbate or reveal a latent diabetes, but because they may cause diabetes when secreted in excess. Phaeochromocytoma Cushing's syndrome and acromegaly are known to be associated with diabetes (Table 2).

TABLE II  
*Incidence of diabetes in endocrine disorders.*

|                         | Frank diabetes | Impaired glucose tolerance |
|-------------------------|----------------|----------------------------|
| Acromegaly .....        | 25%            | 40-50%                     |
| Cushing's .....         | 25%            | 85%                        |
| Phaeochromocytoma ..... | 10%            | 50%                        |

An increased incidence of diabetes is seen too in thyrotoxicosis and glycosuria diminishes when the thyrotoxic state is controlled, though insulin requirements do not always fall dramatically.

Since Professor F. G. Young, extending Houssay's famous studies demonstrated in 1937 that permanent diabetes could be produced in dogs by growth hormone injections, there has been growing excitement over the action of this substance and its possible relationship to human diabetes. Hypophysectomy reduces insulin requirements in diabetes and the well known insulin sensitivity in Addison's disease and panhypopituitarism needs no further comment.

#### *Case 1.*

Miss V. B., a girl of 20, developed diabetes in April 1961 and was stabilized on 80 units of insulin (Lente). In 1962 she was admitted to Nottingham City Hospital with classical xanthoma diabeticorum involving the arms, thighs and buttocks. This was associated with a serum cholesterol of 620 mg.%. She looked mildly acromegalic and on direct questioning admitted to increased size of her extremities over the last three years. X-ray of her skull demonstrated a grossly expanded pituitary fossa. Her heavy glycosuria was poorly controlled even with 200 units Soluble Insulin and was not influenced by a course of high voltage radiotherapy. One month later she developed frontal headaches and a bitemporal visual field defect. Her dose of Soluble Insulin was increased to between 500 and 600 units with only partial control of her glycosuria, though ketosis was never a problem. She was transferred to the Derbyshire Royal Infirmary, where under cortisone cover an extremely large pituitary tumour was removed with difficulty (Mr. *Julian Taylor*). Post operatively her insulin requirements fell dramatically but on the third day her condition deteriorated and she died without regaining consciousness.

On one occasion before operation the average morning blood sugar after 208 units of soluble insulin was 337 mg.%. When insulin was withdrawn altogether the average sugar level over a comparable period rose only to 408 mg.%. This emphasises the marked antagonism to insulin which exists in very active acromegaly. We were also able to demonstrate an increased glucocorticoid and androgen excretion in the urine—no doubt reflecting an increased production of A.C.T.H.—a further cause of insulin antagonism.

It is customary to divide diabetes into the relatively stable adult type and the unstable juvenile type. The latter are thin, sensitive to insulin and when deprived of it, lose weight and develop ketoacidosis. Over 82% of the adult type are, or have been, overweight at the time of diagnosis and characteristically are relatively

resistant to insulin. In the majority the diabetes can be controlled by a reduction of body weight, but if calories are not restricted, large quantities of insulin may have to be given to control hyperglycaemia. Insulin dosage can often be reduced even to zero if such patients can be persuaded to lose weight.

High dosage of insulin in an obese patient, then, seldom indicates a severe diabetic state, but rather a tissue resistance to the action of insulin.

It is well known that insulin requirements rise during ketoacidosis and a clinical impression that insulin works better when ketosis is controlled. This resistance to insulin has now been explained by Field and Stetten's discovery of an antagonist in the alpha-1 globulin fraction of the serum proteins which disappears when the diabetes is brought under control. *Ottoway* (1961) too produced evidence that ketones themselves can act as insulin antagonists.

The older physician often talked of "resting" the pancreas—a term which perhaps emphasised his awareness of the effect of mental and physical stress in exacerbating the disease. Insulin requirements rise during intercurrent infections, coincidental diseases and heart failure. The reasons for this are still obscure though an increased secretion of glucocorticoids in response to stress has been suggested. (*Lawrence, 1926*).

Before discussing true insulin resistance, mention must be made of that most difficult problem, the juvenile labile diabetic with his unpredictable swings of hyper- and hypoglycaemia and a career punctuated by frequent admissions to hospital for restabilisation. Puberty is often a stormy time for the diabetic, and it is tempting to suspect the influence of the growth hormone. *Priscilla White* (1960) has convincingly shown that children who develop diabetes at puberty are heavier and taller than normal though their measurements become normal when diabetes is established. An important phenomenon occurring quite frequently in the early months of juvenile diabetes is the so-called remission. In the context of insulin antagonism it demonstrates the "reverse of the coin".

#### *Case 2.*

Kevin W., aged 14½ years, was admitted to the Derbyshire Royal Infirmary in diabetic pre-coma, and was stabilised on 48 units of Lente Insulin. Over the next three months, however, his insulin requirements fell to zero, and for the following ten months he remained sugar free and required no insulin. Fourteen months after his initial admission, however, he was readmitted with hyperglycaemia and ketosis and once more required insulin (Figure 1).

These clinical observations support the experimental findings that insulin activity is found in the early months but later disappears when R. D. Lawrence's "absolute diabetes" supervenes. Further, it suggests that the insulin antagonism which must exist initially calls forth an increased secretion of endogenous insulin before the B-cells eventually become exhausted. It is fitting to introduce the subject of true insulin resistance by considering the case of a young girl on the brink of puberty.

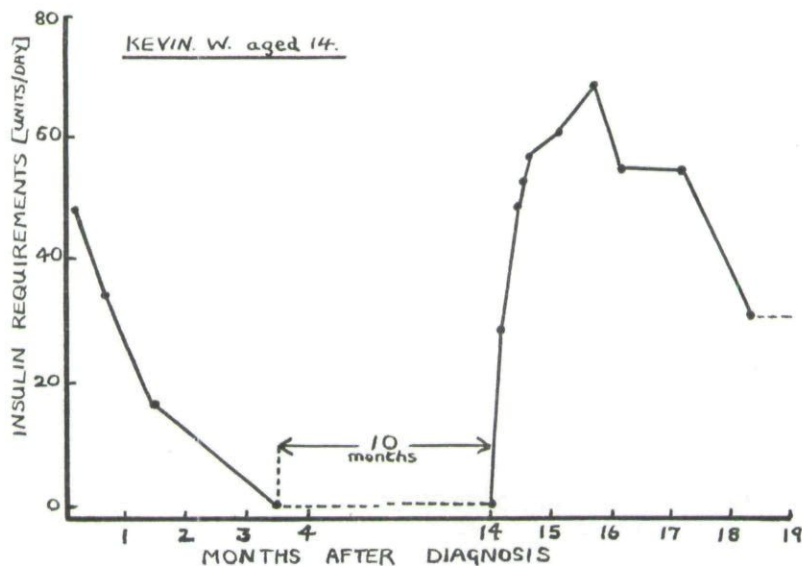


Fig. 1.

## Case 3.

Miss A. B., age 14 years developed diabetes in December, 1951, and was stabilised on insulin. In January, 1953, she was readmitted to the Derby City Hospital for stabilisation. Secondary sexual characteristics were developed but menses had not started. In February insulin resistance developed and continued until April 1st, when 820 units of insulin were given intravenously. At this point she was transferred to King's College Hospital, London, but soon after arrival insulin sensitivity suddenly appeared and she was discharged home. Sensitivity was once more restored, but in June (see Figure 2) she was again requiring large doses of Insulin. Her requirements once more fell but rose again just before her first menstruation in early July. She was very ill and only just survived. A quiet month followed, but resistance returned with the approach of her second period. Again sensitivity was restored in August, but metabolic hell was let loose on the 5th day of her period. At one point she required 9,740 units of insulin daily. In late September there was a brief return of sensitivity and requirements rose sharply to 8,000 units during her fourth period. October was relatively peaceful and her next period was late, though severe and prolonged resistance occurred at this time. When menstruation eventually arrived, again there was severe insulin resistance with a maximum daily dose of 19,250 units. Insulin sensitivity was never fully restored in December and following her late period 18,000 units of insulin were given intravenously. The blood sugar fell but she developed renal failure with anuria, and died on January 16th, 1952.

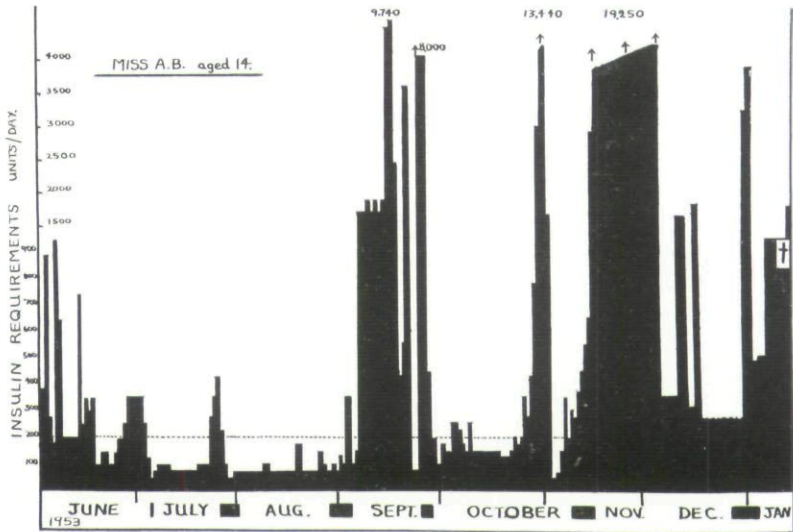


Fig. 2.

This example, already published (*Hubble, 1954*) is I think, unique as an instance of phasic resistance undoubtedly related to the pre-menstrual phase of the menstrual cycle. This variety of insulin antagonism was certainly hormone dependant.

Insulin resistance has been defined by *Root (1929)* as a state in which more than 200 units of insulin are required for more than 48 hours in the absence of ketoacidosis. Fortunately severe insulin resistance is rare (less than 0.1% of all diabetics) but even when relatively mild it can be prolonged and wearisome for both physician and patient.

The following patient spent four months in hospital.

#### Case 4. (Figure 3).

Mrs. B., aged 64 years, developed diabetes in 1957 and one year later was readmitted to the Nottingham General Hospital and stabilised. Her initial insulin requirements were high during her ketotic period, subsided satisfactorily but gradually rose to a level of 260 units. She was allowed home for a month but readmitted with increasing insulin resistance. When her insulin dosage reached 540 units daily Prednisolone, 30 mgms. daily was given. There was a dramatic fall in insulin requirements and within three weeks the crisis was over. Corticosteroids were withdrawn gradually and over the last three years she has remained sensitive to insulin and is now well controlled on 40 units Protamine Zinc and 20 units Soluble Insulin.

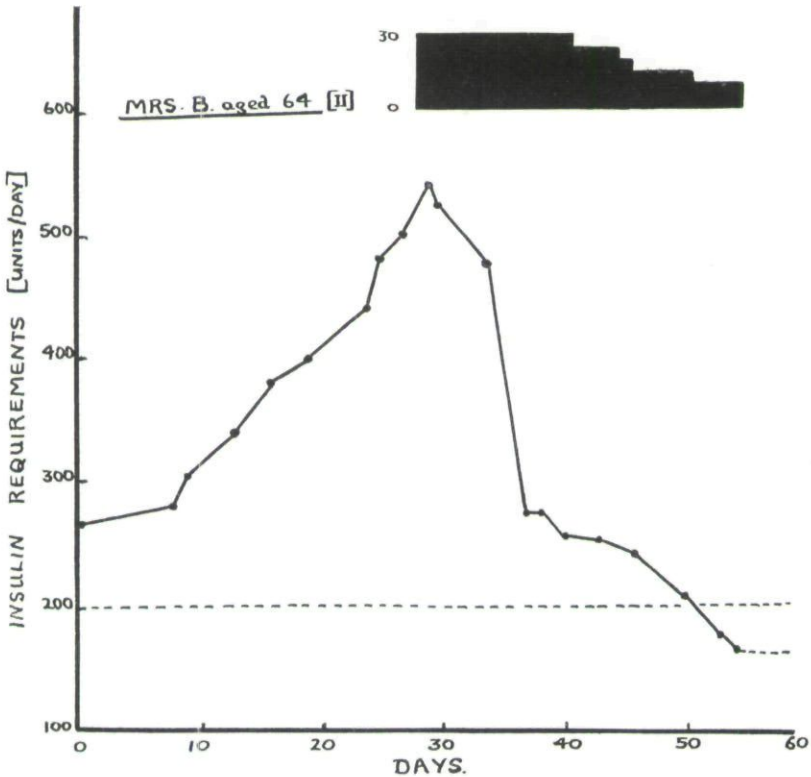


Fig. 3.

Sensitivity to insulin is not always retained, however, and occasionally resistance returns when corticosteroids are stopped. This last case supports the findings of *Oakley* and his colleagues (1959) that resistance usually occurs early in the course of diabetes. Though no special investigations were done, the prompt response to corticosteroids suggests that insulin antibodies were present in excess.

Not all examples of idiopathic insulin resistance respond to corticosteroids, and in such cases control of hyperglycaemia must be achieved by boldly increasing the insulin dosage until sensitivity returns. It may however return with surprising suddenness and cause severe hypoglycaemia, due to a sudden and unexplained release of insulin from its binding protein. There is no certain way of preventing insulin resistance but there is some evidence that either prolonged hyperglycaemia or frequent attacks of hypoglycaemia may provoke insulin antagonism so that optimum control of the diabetes is all important.

Several reports have now appeared of severe resistance in which insulin-like activity has been demonstrated in the serum (*Dowling*, 1957; *Leonard & Martin*,

1959, Field, Weinberg, Johnson & Spoont, 1959, Shipp, Russell, Steinke, Mitchell and Hadleys, 1961) and it has been suggested that in such cases the insulin is either unable to reach the cells in an active form or that the cells themselves are unresponsive.

Occasionally co-existing disease, though present, may be difficult to spot as illustrated by the next example of insulin resistance.

Case 5. (Figure 4).

F. S., a man of 54 years, had suffered from alopecia totalis for 20 years. He developed diabetes mellitus in December, 1961, and was stabilised on 76 units of Lente Insulin. He remained well until March, 1962 when he was readmitted to the General Hospital Nottingham, with uncontrolled diabetes. He settled down initially following treatment with Soluble Insulin and intravenous fluids, but during May, 1962, his insulin requirements gradually rose to between 400 and 600 units. It was then noticed that his liver had become enlarged and spleen tip just palpable. Liver function tests revealed an alkaline phosphatase of 21 K. A. units and a S.G.P.T. of 200 units. A liver biopsy showed the typical appearance of haemochromatosis with iron in the liver cells, K  pffer cells and portal tracts with some evidence of cirrhosis. His serum iron was normal (144 mg %. 150

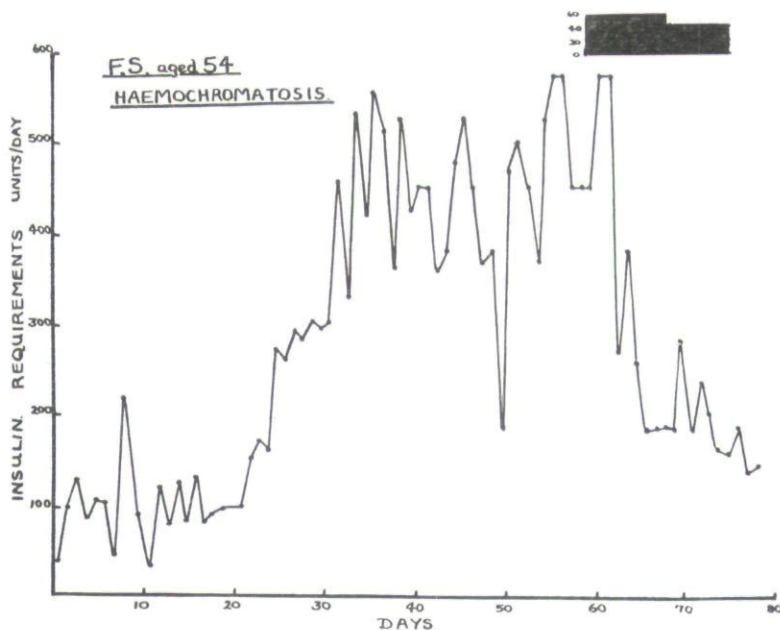


Fig. 4.

mg%) and unsaturated iron binding capacity 74 mg% (67 % saturation). Clinically the patient was fair skinned with no trace of abnormal pigment. A skin biopsy, however, showed traces of iron in the sweat glands. Studies with radioactive iron demonstrated an absorption of 55% of an administered dose confirming the diagnosis of haemochromatosis.

As his insulin requirements were steadily rising and his clinical condition deteriorating, he was started on Prednisolone, 60 mgms. daily. Within two weeks his requirements fell and over the next three months corticosteroids were gradually reduced to zero.

Dr. *Vallance-Owen* was unable to detect insulin antagonism in the plasma albumen fraction of a blood sample taken before corticosteroids were started.

*Sheldon* (1935) in his classic work observed that glycosuria occurs in 78% of patients with haemochromatosis. Insulin requirements are often high, but resistance as defined by *Root* occurs in only 3%. This is probably an understatement as haemochromatosis often goes unrecognised.

#### *Case 6.*

Mr. T. J., aged 69 years, developed diabetes mellitus in 1954 and was stabilised on Lente Insulin, 12 units. Seven months later inspite of 52 units of insulin he continued to lose weight and was admitted to the Nottingham General Hospital for stabilisation. His liver was grossly enlarged and found to be cirrhotic on peritoneoscopy. Liver function tests indicated mild hepatocellular damage but skin pigmentation was not present. Over a period of three weeks in hospital heavy glycosuria continued without significant ketosis and his insulin requirements gradually rose to a maximum of 260 units. Sensitivity was eventually restored without response to corticosteroids. Three years later he was admitted with pneumonia which proved fatal. Autopsy revealed cirrhosis of the liver and the classical appearance of haemochromatosis.

*Colwell & Weiger* (1956) studied an insulin-resistant patient with haemochromatosis who responded to A.C.T.H. and they suggested that the rise in gammaglobulin which occurs in liver disease and which is reversed by steroids may be connected with the development of insulin resistance. It is my impression that liver disease figures prominently in post-mortem reports of examples of insulin resistance and is not uncommon in those who survive. Any hint of liver disorder should certainly be followed up with a liver biopsy, as haemochromatosis can be present without skin pigmentation and the presence of a normal serum iron. Weekly venesection in this condition can prolong life, minimise the cirrhosis and alleviate the diabetes.

In dealing with any disease one is faced with a patient, and the first essential of good medical practice is the acceptance of this patient's story. The following "cautionary tale" concerns a psychopath who betrayed her physician's trust.

*Case 7.*

Miss P. B., a ward sister aged 27, developed diabetes in 1958. From 1960-1962 she had apparently required between 600 and 800 units of insulin daily. After her admission in March, 1962 for stabilisation her insulin requirements gradually rose until she was having 1,500 units daily. She became such a difficult problem that she was transferred to a special unit where, for three months her insulin requirements were apparently between 1,000 and 2,000 units daily. It was then discovered that she had practised a deception, had been manipulating her insulin, faking her temperature and hoarding her tablets in her handbag. She had multiple intravenous infusions, developed a deep vein thrombosis and possible pulmonary embolism, underwent a laparotomy and knowingly exposed herself to the risk of severe hypoglycaemia when large amounts of intravenous insulin were given. It appeared that her true insulin requirements were probably no more than 90 units. Had this patient died during this strange "adventure" she may well have gone on record as a unique example of insulin resistance with insulin-like activity in her serum.

Exogenous insulin, being a foreign protein is mildly antigenic and insulin binding globulins have been demonstrated after prolonged insulin therapy. (*Berson, Yalow, Bauman, Rothschild and Newerly*, 1956). These antibodies bind pure beef insulin 7-10 times more actively than pork insulin (*Berson & Yalow*, 1959) and this may well be related to the minor species differences in chemical structure which have been demonstrated (*Young*, 1961). Eight examples are now on record of resistance to beef insulin with sensitivity to pork insulin. (*Boulet, Mironze, Bonjon and Schmonker*, 1959; *Derot and Rathery*, 1959; *Kissel and Bebry*, 1959; *Kreutzer, Moors and Verhille*, 1961; *Goldman and Kaye*, 1962). This form of therapy, however, is usually limited by lack of available pork insulin.

Although insulin resistance may co-exist with insulin allergy, both occur independantly. (*Lowell*, 1944). Allergic reactions may be local at the injection site and usually occur during the first weeks of insulin therapy. Many reactions in the past were due to protein impurities but occasional reactions are certainly due to insulin itself or the protein with which it is associated.

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<sup>1</sup> This patient probably falls into the category of Munchausen's syndrome. Ref.: *Clarke & Melnick*, 1958.

Very rarely a generalised reaction is seen, usually when insulin therapy is resumed after an interval (*Hanauer and Batson*, 1961) or when very large amounts are given in severe resistance. (*Hubble*, 1954). Insulin resistance is rarely due to poor absorption from an area of lipodystrophy—the result of frequent injections into the same site.

The purpose of this paper has been not only to emphasise and illustrate some clinical aspects of insulin resistance and antagonism but also to underline the complexities of diabetes itself. I will conclude by quoting from a leader in the *B. M. J.* "We now know that the metabolism of carbohydrate, of fat, and of protein, are interrelated and regulated by a balance of hormones rather than each simply by one hormone. Diabetes mellitus represents a disorder of this regulation and involves not only a lack of insulin but also an overaction of the antagonists of insulin". (*Brit. Med. J.* 1961).

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