I wish to thank Dr. J. W. Brown, Dr. C. S. Darke, Dr. K. J. G. Milne, Dr. E. G. Rhind, and Professor C. H. Stuart-Harris for permission to examine and study patients admitted under their care; Dr. E. K. Abbott for her help with the radiographs and screening; Dr. M. Pownall for the bacteriology; Dr. E. Glazowski, Dr. T. Southgate, Dr. T. Tlusty, and Dr. A. J. N. Warrack for the necropsies; Dr. S. Varadi for the haematology; the medical registrars, house-physicians, and ward sisters whose co-operation made this investigation possible; Mr. A. S. Foster, medical artist to the United Sheffield Hospitals, for drawing the figures; and Miss M. Emery for secretarial assistance. I gratefully acknowledge the helpful criticism which I have received from Dr. B. Burns, Dr. K. J. G. Milne, and Professor C. H. Stuart-Harris in the preparation of the manuscript.

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INSULIN RESISTANCE

BY

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Insulin resistance in diabetics is usually defined as a state in which more than 200 units of insulin daily are required to lower the blood sugar to normal levels, such resistance being maintained for not less than 48 hours. This definition, although arbitrary, may be usefully retained until the nature of insulin resistance is understood. It is well recognized that infection and ketosis increase insulin requirements and that insulin resistance is present in some patients in diabetic coma, though whether the involved mechanisms are related to the insulin resistance which occurs in the absence of these states is quite unknown.

It is also recognized that the young insulin-sensitive diabetic oscillates rapidly from hypoglycaemia to hyperglycaemia and ketosis, even under controlled conditions in hospital, and in the absence of infection or other relevant environmental disturbance. In such children there is also a notable disposition to nocturnal hyperglycaemia. Payne (1953) has found that this instability of insulin control is not uncommon in diabetic girls at puberty, and that it can sometimes be avoided by a small dose of oestrogen given in the premenstrual phase.

Smelo in 1948 reviewed 54 cases of insulin resistance in the English literature to that time. Only two of these cases occurred in children. For the entire series of 54 cases, Smelo records a death rate of 41%. He regards the prognosis of the condition as relatively benign, however, and suggests that more careful control and the use of larger doses of insulin would achieve more successful results.

Joslin *et al.* (1952) listed a further 20 cases from the New England Deaconess Hospital, and two of these were in children. The first a boy of 12 years, whose resistance lasted for 8–10 days and required a maximum of 210 units daily; the second a girl of 14 years, whose resistance lasted more than one year and whose maximum requirement of insulin was 470 units daily. The boy's resistance was associated with an allergic sensitivity to all insulins except the crystalline variety, and the girl's resistance was associated with abscesses on the thigh.

Although children are commonly classified as insulin-sensitive, it is by no means uncommon for them to require more insulin for stabilization of their blood sugar than would be regarded as their expected pancreatic secretion. Although this insulin resistance is commonly taken to be due to the action of contra-insulin hormones, as in diabetic girls at puberty, there is no objective evidence for this. In fact, the only exact hint regarding the possible mechanisms involved in insulin resistance derives from Bornstein's work (1953). He injected into insulin-resistant patients 300 units of crystalline insulin intravenously, and by his method of insulin assay was unable in one hour to demonstrate any insulin in the plasma.

There is now to be related the unhappy history of a diabetic girl whose insulin resistance was of a degree hitherto unrecorded, and in whom the resistance was phasic. The resistant phases appeared to be premenstrual and the phases of insulin sensitivity appeared to succeed the menstrual flow.

An Extreme Case of Insulin Resistance

A.B., aged 13 years, a grammar-school girl, was admitted to the children's ward of the Derby City Hospital on December 10, 1951, suffering from diabetic ketosis. The symptoms of diabetes had been present for two months. She recovered without the use of intravenous saline and was discharged from hospital on December 23—requiring 24 units of soluble insulin twice daily. Her maternal grandmother was said to suffer from diabetes. Her height at this time was 5 ft. 4¾ in. (164 cm.), which was four inches (10 cm.) above the average height for a girl of her age. The secondary sex characters were just appearing, but menstrual function was not established.

She attended the children's diabetic clinic at the Derbyshire Hospital for Sick Children during the following year and made excellent progress. Her insulin needs were increased to 60 units of soluble insulin daily in two injections. She was readmitted to the Derby City Hospital on January 9, 1952 (thirteen months after her original admission), for restabilization on a mixture of soluble and zinc protamine insulin. Her height had increased in 1952 by ¾ in. (1.9 cm.) to 5 ft. 5½ in. (166 cm.) and her weight was 8 st. 9 lb. (54.9 kg.). The secondary sexual characters were now fully developed, but the menses had not occurred. Early-morning hypoglycaemia developed with a dose of zinc protamine insulin as small as 8 units, so a mixture of globin insulin 24 units and soluble insulin 28 units was used for a time. In six weeks in hospital she had gained 8 lb. (3.6 kg.) in weight, so her daily ration of carbohydrate (which had previously been "free" except for the restriction of jams, sugar, and sweets) was reduced to 250 g.

On February 26, 1953, while still in hospital, persistent hyperglycaemia developed and she was treated by injections of soluble insulin three- to four-hourly. Despite a steady increase of dosage during the next three weeks, to the amount of 12,160 units by March 20, her blood sugar was seldom below 250 mg. per 100 ml. in the daytime, nor did sugar disappear entirely from the urine. There was intermittent

ketosis, but her general condition remained good. During the succeeding few days, because of the difficulty of breaking down this resistance by increased dosage (the injection of 40 ml. daily with an insulin concentration of 320 units per ml. was already creating problems) it was decided to reduce her insulin dosage to 80 units four-hourly. This was continued till March 24, when Professor D. M. Dunlop kindly saw the patient with me and suggested the use of intravenous insulin. For a few hours this procedure was effective and her blood sugar was reduced from 520 mg. at 4 p.m. to 253 mg. per 100 ml. at 10 o'clock the next morning, and a further 80 units of intravenous insulin reduced it to 145 mg. per 100 ml. This success was brief. On March 26 280 units, on the 27th 240 units, on the 29th 420 units, on the 30th 680 units, and on April 1 820 units were given intravenously. On April 2 Dr. Wilfrid Oakley agreed to accept the responsibility for her treatment, and she was admitted under his care at King's College Hospital. She travelled to London by car with her mother and was ill on the journey with some vomiting; on arrival she was acidotic and ketotic but her blood sugar was only 75 mg. per 100 ml. She was treated by intravenous saline, gastric lavage, and small doses of soluble insulin. Insulin sensitivity was restored and she was discharged from King's College Hospital on April 12, having two doses of soluble insulin (28 and 24 units) each day. Insulin sensitivity continued for two weeks, but hyperglycaemia again developed, and it was necessary to readmit her to the Derby City Hospital for treatment of pre-coma on May 16.

On readmission insulin sensitivity was restored by intravenous saline, continued for two days, and a maximum dose of 350 units of insulin in one day. Insulin resistance again developed, and she required intravenous saline on June 2 (two days) and on June 13 (three days). The maximum daily dose of insulin in this month was 800 units on June 8. Hyperglycaemia and ketosis developed again towards the end of the month, and intravenous saline was required from July 3 to 5. On July 6 vaginal haemorrhage occurred for the first time, and from then until July 23 all was quiet and the blood sugar was easily controlled with 100 units daily or less. On July 23 the storm broke without warning; her morning blood sugar was 100 mg. per 100 ml., but by evening she required intravenous saline, which it was necessary to continue for four days. She was very ill and only just survived. There was slight vaginal haemorrhage during the last two days of this ketotic period and menstruation was fully established for two days on recovery.

A quiet month followed, and when the next menstrual period began on August 28 without consequent rise of blood sugar, anxiety was relieved. On the fifth day of the period hyperglycaemia and ketosis developed and intravenous therapy was required for two days. On this occasion insulin sensitivity was not restored, and daily insulin dosage climbed to 9,740 units on September 17, fell, and climbed again to 8,000 units on September 24. This, however, was the first day of a three-day menses, and once again insulin sensitivity was restored.

During the summer both stilboestrol and ethinyl oestradiol were used in treatment, but with no good result that could be seen, and their use was discontinued. As will be readily appreciated, hypoglycaemic reactions gave rise to much therapeutic difficulty when insulin sensitivity was restored with these enormous doses of insulin—and one feature of this hypoglycaemic state which was troublesome was the persistence of "hysterical" hyperventilation long after the acidosis and electrolyte imbalance had been corrected. On another occasion the appearance of meningismus required the performance of a lumbar puncture, as there were cases of lymphocytic meningitis in the ward at the time. The patient was in fact a charming, stable, and intelligent creature, but these violent fluctuations in blood sugar now and again played havoc with her psyche. In July thrombophlebitis and urticaria developed during a ketotic phase, and this trouble, though it recurred later, was never more than might have been expected to result from repeated intravenous therapy and the large doses of insulin employed.

October was an insulin-sensitive month, although her daily needs were between 1 and 200 units. The menses were late, and 13,440 units were required on November 1. Menstruation occurred on the 9th (a six-weeks interval), and on the fifth day of her period she required 7,480 units. On November 27 she required, for the first time in three months, intravenous saline for four days; and on November 30 she had a one-day period. During the month of December her insulin needs increased again to a maximum of 8,640 units daily, but a further complication occurred with the development of abscesses at the sites of insulin injection. These came up slowly, and many of them required incision. Haemolytic streptococci were isolated from the abscesses. Some of the incisions produced only serum and fat globules.

The story of the last two months of her life is told in the Table. Insulin sensitivity was never fully restored in December. Hexamethonium bromide was used in doses of

Analysis of the Last Two Months of Treatment

Date	Urinary Endocrine Assays (24-Hr Periods)				Daily Insulin	Ketosis	Menstruation	Sepsis	I-V. Saline
	Oestrogens	Pregnanediol	17-Ketosteroids	17-Ketogenic Steroids					
		mg.	mg.	mg.	u.				
6/11/53	20 i.u.	0·5	9	18	130	O	9/11/53		
11/11/53			10	16	370	O	|		
13/11/53			9	20	640	O	|		
16/11/53	None	0·75			7,480	K	16/11/53		
20/11/53	,,	0·6	9	17	3,840	K			
24/11/53	,,	0·5			19,200	K			27/11/53
27/11/53	50 i.u.	0·7	5	7	11,840	K			|
30/11/53	40 i.u.	0·9			9,760	K	30/11/53		|
5/12/53	Trace		10	23	360	O	|	5/12/53	30/11/53
6/12/53	,,	0·8	7	3	300	O	|	|	|
11/12/53					1,680	K	|	Abscesses	|
14/12/53	None				310	O	|	|	|
16/12/53			4	21	1,800	O	|	|	|
18/12/53	30 i.u.				280	O	26/12/53	22/12/53	24/12/53
31/12/53			7	4	3,220	O	|		|
1/1/54	None				3,840	K	|		25/12/53
3/1/54	,,				4,800	K	3/1/54		
6/1/54			3	8	510	O			
7/1/54	Trace				960	O			
13/1/54			9	16	1,800	K			

This table relates endocrine output to the menstrual cycle and to the insulin-resistant phases. It will be noted that there is a gap from December 19 to 30, a premenstrual period of progressive ketosis and increasing insulin requirements up to 8,640 units daily, eventually requiring intravenous saline.

25 mg. and 12.5 mg. by injection, with the object of potentiating the effect of insulin, and for a few injections this method appeared to be remarkably effective. It soon failed and was discarded. After the late December period some degree of insulin resistance remained, and, in view of the subcutaneous abscesses at the sites of injection which had already been so troublesome, very large doses of insulin were not used. Ketosis recurred on January 13 and a state of pre-coma required intravenous saline. Insulin was given intravenously, and in one day 18,000 units was administered by this route with proper precautions. The blood sugar fell, but the blood urea mounted and renal failure and anuria supervened. It seems possible that the intravenous administration of insulin accelerated the development of shock nephrosis. Death occurred on January 16. Necropsy showed the characteristic tubular changes in the kidneys, but no structural disease in the endocrine system was discovered.

Discussion

From July 6, 1953, to January 16, 1954, the patient required five periods of administration of intravenous saline. In four instances the intravenous saline immediately preceded menstruation, and on one occasion saline was required on the sixth day of the period. The September and October menses were not preceded by intravenous therapy, but in the nine days preceding the September menstrual period 30,720

units of insulin were given, and in three days (9th–7th days) before the November period 18,200 units were required.

Insulin sensitivity was restored immediately after the July, August, September, late November, and December periods, but after the early November menses, which lasted a week, insulin resistance persisted despite a dose of 19,200 units in one day. With these exceptions it may be concluded that insulin resistance was associated with the pre-menstrual phases and insulin sensitivity with the post-menstrual phases. The pre-menstrual phase of insulin resistance varied from 3 to 18 days and the insulin-sensitive phase from two days (menstrual cycle of 20 days) to five weeks (menstrual cycle 46 days).

There can be little doubt that the insulin resistance was hormonal and related to the pre-menstrual phase of the menstrual cycle. Before menstruation was established in May and June (and in April when she was in King's College Hospital) it appeared that insulin sensitivity was restored by the treatment of ketosis by intravenous saline and by frequent insulin injections. This may well have been an incorrect conclusion, and the restoration of insulin sensitivity may have been dependent on a hormonal change not as yet followed by menstruation. The hormones which might possibly be concerned in such resistance are the growth hormone, the corticosteroids, glucagon, the oestrogens, or progesterone. There is no evidence that the female sex hormones can produce an insulin resistance of this degree. The increased insulin requirements of the diabetic woman in pregnancy are well recognized, but they are not of this grandiose nature despite the much greater formation of sex hormones in pregnancy than occurs in the menstrual cycle. The urinary output of the sex hormones was not increased and there was no correlation between the variations in oestrogen and pregnanediol output and insulin needs (see Table). The considerable fluctuations in the daily urinary output not only of oestrogens but also of 17-ketosteroids and 17-ketogenic steroids perhaps portrays the unstable hormonal state of this pubertal girl which was reflected in the diabetes.

The corticosteroids antagonize indirectly the action of insulin and are gluconeogenetic, but there is now increasing evidence that they are not important in the aetiology of diabetes apart from that occurring in Cushing's syndrome. Cortisone has been frequently used in diabetics with no considerable increase of insulin needs. The 17-ketogenic steroids (Norymberski, 1952) are stated by Norymberski, Stubbs, and West (1953) to represent a little less than half the 17α-hydroxycorticosterone output (hydrocortisone, Kendall's Compound F). There was considerable variation of the corticosteroid output (see Table), and it was sometimes raised above normal levels, but not greatly. Nor was the highest output related to the periods of ketosis, as in the cases reported by Stowers (1951). There is no evidence that the adrenal cortex played an important part in the insulin resistant diabetes of A.B. And the fact, commented on below, that her growth was excessive during the year of insulin resistance speaks strongly against adrenocortical influence.

Glucagon has not established itself as a hormone, nor has its place, if any, in the aetiology of diabetes been determined, so that it may be excluded from consideration. In a series of remarkable researches each new fact sustaining a brilliant generalization, F. G. Young and his colleagues (1951) have proved that the growth hormone is diabetogenic in carnivorous animals. Unfortunately no assay of the growth hormone is available in man, so that clinical evidence in favour of Young's hypothesis is indirect. Priscilla White (1952) was the first to make the observation that the height of diabetic children was greater than average for their age and sex. A.B. was 4 in. (10 cm.) above the average height for her age at the onset of diabetes. In the year of stability, 1952, she grew $\frac{3}{4}$ in. (1.9 cm.); in the year of increasing insulin resistance, 1953, she grew $2\frac{1}{2}$ in. (6.3 cm.). Nothing is known of the output of the growth hormone in the varying phases of the menstrual cycle; nothing is known of the variations in the internal environment which may affect its output. Nevertheless, there is indirect evidence that the growth hormone was remarkably active in A.B. during 1953.

The development of a local reaction to insulin at the sites of injection, followed by some sepsis, no doubt enhanced the insulin resistance during the last two months of her life. It also had the effect of making me more reluctant to use again the large single subcutaneous doses (10 ml. × 320 units per ml.) which were used in September. The use of intravenous insulin in the final ketotic episode may have hastened the end.

There has been much debate for many years on whether insulin used in excessive doses may itself encourage hyperglycaemia, both in the treatment of diabetic ketosis and in the maintenance therapy of diabetes. The daily injection of insulin in the rat has caused reduction of the growth of the islets of Langerhans (Evans and Haist, 1951), and no one would wish to use more insulin than is necessary to maintain the diabetic's blood sugar near normal limits. There are complicating factors in diabetes—obesity, infection, and electrolyte imbalance—and when these are adequately controlled insulin requirements are reduced. There were, however, other undefined complicating factors as in A.B., and until some other means of opposing them is discovered insulin must be used in dosage which is adequate both to reduce the blood sugar and to prevent ketosis. On many occasions and for long periods frequent small doses of insulin were used in our patient in the hope of not provoking the action of contra-insulin phases. This method was unsuccessful.

Summary

An example of unique insulin resistance in a young diabetic girl is recorded. The maximum daily dose of insulin used was 19,250 units. The resistance was phasic, and when menstruation was established it was seen that the resistant phases were usually premenstrual and the sensitive phases post-menstrual.

A large number of urinary endocrine assays were made, and although these fluctuated considerably they showed no remarkable deviation from average findings.

It is assumed that the growth hormone had a hand in this insulin resistance. The patient was 4 in. (10 cm.) above the average height at the onset of her diabetes, she grew an average amount in a year of stability, but in the year of insulin resistance she grew nearly 2 in. (5 cm.) more than the average for her age—0.7 in. (1.8 cm.).

The correct treatment of insulin resistance is to overcome the resistance by using insulin in adequate dosage.

I am grateful to Dr. W. G. Oakley, who treated the patient in King's College Hospital during one of her ketotic phases; to Professor D. M. Dunlop, who helped me with his experience of insulin resistance; to Dr. C. G. Paine, Mr. F. L. Mitchell, Ph.D., and Mr. M. J. Level, B.Sc., of the Endocrine Laboratory, Jessop Hospital for Women, Sheffield, who performed the urinary endocrine assays; to Dr. Ann Ferguson, paediatric registrar, and my house physicians, Drs. J. Forsyth and M. W. Dickson; and to the sisters and nurses in the children's ward at the City Hospital, Derby, who were unremitting in their care of the patient.

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