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Review Articles

Insulin Deficient Diabetes

Contrasts with Other Endocrine Deficiencies*

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Summary. Comparisons are made between the incidence, prognosis and treatment of juvenile-onset diabetes and other endocrinopathies in the young. 548 patients with insulin deficient diabetes diagnosed before 20 years of age have been reviewed. Excess mortality, especially at 35–40 years of age was found. Profiles of blood glucose and serum insulin have been studied and compared to those of normal subjects. The variation of insulin absorption and effect of insulin antibodies on the free insulin levels achieved after exogenous insulin injection have been demonstrated. The common occurence of nocturnal subclinical hypoglycaemia following intermediate or long-acting insulin was often found to be the cause of poor diabetic control. Five out of 33 patients with 'difficult' diabetes had an unexplained resistance to high levels of free-insulin. The value of self-monitoring and HbAl measurements in the improvement of diabetic control and possibly life expectation is reviewed. The incidence of thyroid disease was found to be increased in 1779 insulin deficient diabetics of all ages and persistence of islet-cell antibodies suggests that the diabetes may be due to autoimmunity in some of these patients.

Key words: Insulin deficient diabetes, islet-cell antibodies, free insulin concentration, autoimmune diabetes mellitus, Self-monitoring of blood glucose, HbAl.

Patients with hormone deficiencies respond well to the replacement therapy that is now available. It is only in insulin deficiency that long-term complications seem to occur. To some extent this may represent lack of ascertainment because there is little information available on the long-term follow-up of such conditions as juvenile hypothyroidism. The figures given in Table 1 are for patients seen in the wards and general endocrine and diabetic out-patient clinics of the Middlesex Hospital, London between 1954 and 1978. Also included are patients seen elsewhere by one of the authors (JDNN). The total number of diabetics seen during this period was 5536, of these 3757 were regarded as being non-insulin dependent: it is the policy of this clinic only to use insulin when absolutely essential. These figures (Table 1) highlight the rarity of other types of hormone deficiency in young people.

Table 1. Patients with endocrine deficiency states

		Total	Age of onset under 20 years
Thyroid	– Primary	203	19
	Iatrogenic	74	
Parathyroid	– Primary	2	1
	Iatrogenic	47	
Adrenal Cortex	– Primary	41	4
	Iatrogenic	105	2
Gonadal failure	– Primary	65	65
Anterior Pituitary	– All hormones	140	8
	Gonado-trophins	68	60
	Gonado-trophins + growth hormone	7	7
	Growth hormone	4	4
	Iatrogenic	106	
Diabetes insipidus		55	11
Insulin deficiency		1,779	548

* Based on the 29th Banting Memorial Lecture delivered to the British Diabetic Association, 15th September, 1978

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Table 2. Incidence of auto-immune disease in 1,779 patients with insulin deficient diabetes

Hyperthyroidism	54
Hypothyroidism	42
Thyroid eye disease	2
Hashimoto thyroiditis	4
Pernicious anaemia	8
Vitiligo	5
Addison's disease	2
Primary biliary cirrhosis	3
Disseminated lupus erythematosus	1

Table 3. Incidence of hyper- and hypothyroidism in insulin deficient diabetes

	IDD	Population survey[a]	Significance
Number	1,779	2,779	
Hyperthyroidism	54 (3.0%)	44 (1.6%)	$p < 0.005$
Hypothyroidism	42 (2.4%)	23 (0.8%)	$p < 0.0005$

[a] Data from "The Whickham Study" [9]
IDD = insulin deficient diabetes
Significance assessed by the Chi-Squared test

For most of these hormone deficiency conditions, simple oral replacement therapy is used. Vitamin D preparations are used instead of parathyroid hormone for hypoparathyroidism and the synthetic steroid fludrocortisone as a salt retaining steriod in Addison's disease because aldosterone is ineffective when given by mouth. A long-acting analogue of antidiuretic hormone is given by nasal insufflation for diabetes insipidus. Replacement therapy by injection is seldom required, a monthly injection of long-acting testosterone is the most effective treatment of male hypogonadism, injections of gonadotrophin may be used for induction of ovulation in some women and growth hormone deficient dwarfs have to have their treatment by injection for a few years.

For patients with insulin deficient diabetes the hormone has been available for over 50 years, but treatment is not satisfactory. In no way is this intended to belittle the fantastic change that the discovery of insulin has made to the young diabetic. However, he or she still needs to inject the insulin and cannot expect to achieve a normal life span.

There are a number of factors which make insulin deficiency a 'special' case. One is the metabolic consequences of insulin deficiency, a second is the fluctuation of insulin level during the day and from day to day depending on carbohydrate intake, a third the fact that insulin is normally released into the portal venous system and has perhaps physiologically its predominant action on the liver whereas it has to be injected peripherally so that all the tissues are exposed to its action and the liver is not subjected to a higher concentration. Possibly, a fourth factor should also be considered that many insulin preparation have been impure and insulin treated patients have had varying levels of antibodies to insulin in their blood which have influenced free insulin concentrations.

Insulin Deficient Diabetes, Autoimmunity and Association with Other Endocrine Disorders

The first evidence that autoimmunity might be a cause of endocrine disease was obtained by Roitt, Doniach and others in 1956 [1]. Since that time, many workers have tried to find a similar mechanism in insulin deficient diabetes. The increased incidence of thyroid and gastric parietal cell antibodies in patients with diabetes has been well documented [2]. Cellular autoimmunity in diabetes was recognised in the early 1970's [3, 4] and humoral antibodies shortly afterwards [5, 6]. It seems unlikely, however, that the islet cell antibodies present in patients with insulin deficient diabetes are the cause of the condition. In the early stages of the disease they are present in a very high proportion of patients [7, 8], but they disappear rapidly and by the time the patient has had the condition for 10 years, the incidence has dropped to 10%. There are, however, a small proportion of patients in whom the islet cell antibodies persist apparently indefinitely. Many of these patients have other organ specific auto-antibodies and sometimes evidence of other endocrine deficiency states particularly hypothyroidism and Addison's disease [8]. It is reasonable to postulate that in this small group of insulin deficient diabetics the condition really is the result of the organ specific antibodies although it must be pointed out that the antibodies seem to react with all islet cells and not just the β-cell.

In the series of 1779 insulin deficient diabetics referred to in Table 1, the incidence of thyroid and other auto-immune disorders has been reviewed (Table 2). Using data from the Whickham study [9], it can be shown that the incidence of hyper- and hypothyroidism is significantly greater in insulin deficient diabetics than in the general population (Table 3). Many of these patients were seen before it was possible to detect islet cell antibodies, but islet cell antibodies have been sought in a proportion of them by Dr. G. F. Bottazzo and Professor D. Doniach and the incidence greatly exceeds the 10% figure for

Table 4. Persistent Islet Cell Antibodies (ICA) in patients with insulin deficient diabetes and autoimmune disease

Autoimmune disease	Number tested for ICA	ICA + ve	%
Hypothyroidism	25	11	44
Hyperthyroidism	21	10	48
Pernicious anaemia	5	2	
Vitiligo	4	3	
Hashimoto's disease	3	2	
Primary biliary cirrhosis	3	1	

diabetics of more than 10 years' duration (Table 4). These workers have recently reported similar findings in a different group of diabetic patients [10].

Diabetes Diagnosed before 20 Years of Age

Reference has already been made to the unfortunate fact that young people who develop insulin deficient diabetes have a reduced life expectation. The 548 patients in this age group have been reviewed. The age of onset of the condition is shown in Figure 1, it will be noted that the peak age is a little later than that reported by Bloom and others [11]. This may be the result of more consistent reporting by pediatricians. The duration of follow-up since the onset of the condition is shown in Figure 2. Those known to be dead are also indicated. These figures are open to criticism because some patients may only have been referred because of complications, whereas others may have continued to survive without any complications. The gravity of the situation is, however, emphasised by the excess mortality shown in Figure 3 – in the 35–40 year age group, the death rate is 13.9 times that expected. MacGregor [12], gave an equally depressing report of seven deaths in 45 children who developed diabetes before they were 12 and who had been followed for between 12 and 27 years. The overall picture is very similar to that recently reported from Denmark in a 40 year follow-up of young diabetics [13].

The cause of death in these patients is shown in Table 5. The high incidence of death from hypoglycaemia is notable: in the three patients in whom this followed hypophysectomy for retinitis, pituitary surgery had had excellent results as far as preservation of vision was concerned, but, in retrospect, they should probably not have been selected for this form of treatment as they were single men. They were treated before light coagulation became available. The figures given in Table 6 suggest that those with onset between 5 and 9 years of age may live a little

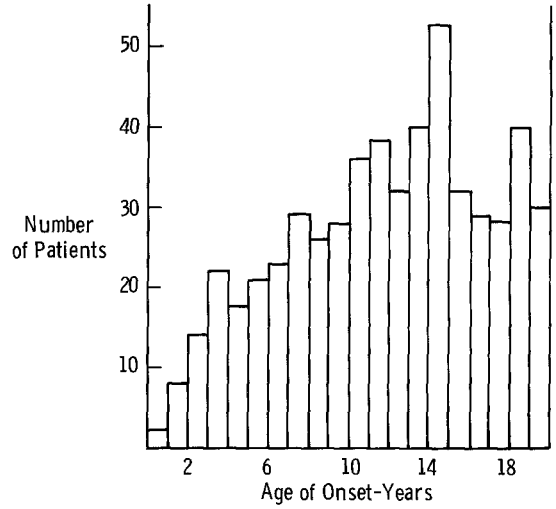

Fig. 1. Age of onset. 548 Insulin-deficient diabetics with onset before 20 years

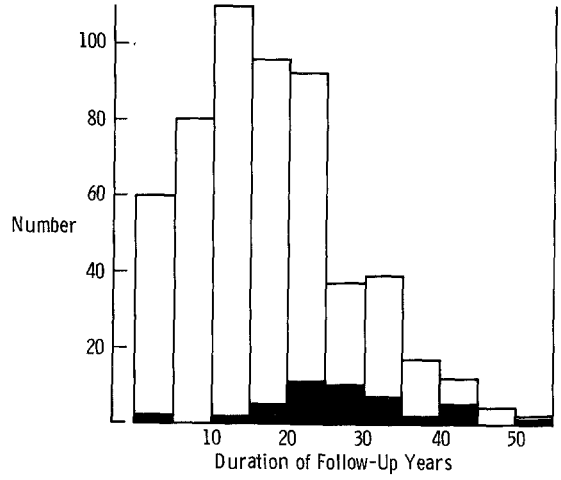

Fig. 2. Duration of follow-up. Patients known to have died shown in black

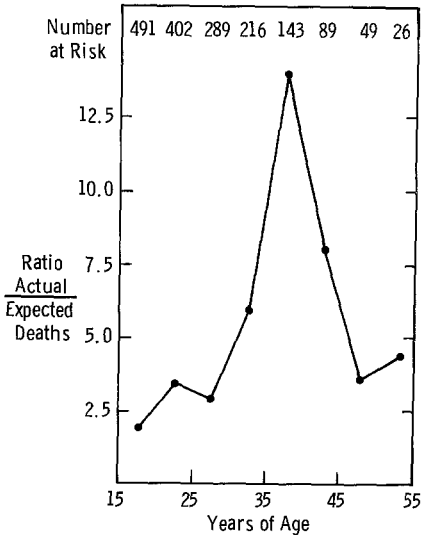

Fig. 3. Excess mortality. Based on figures for 1974 published by the Office of Population Censuses and Surveys

Table 5. Cause of death in 46 patients with insulin deficient diabetes with onset before 20 years of age

Renal failure	16
Coronary artery disease	8
Hypoglycaemia[a]	6
Neoplasm	4
Road traffic accident	3
Cerebrovascular disease	2
Ketosis	2
Suicide	2
"Sudden death"	2
Following hypophysectomy	1

[a] In 3, hypophysectomy had been done for proliferative retinopathy

Table 6. Death and blindness in insulin deficient diabetes with onset before 20 years of age. Relation to age of onset

Age of onset years	Number	Dead	Mean age at death years	Range years	Number blind	% Blind
0–4	64	7	28	16–39	7	11.0
5–9	127	9	40	22–62	16	12.6
10–14	198	19	38	23–54	13	6.5
15–19	159	11	39	21–51	9	5.6

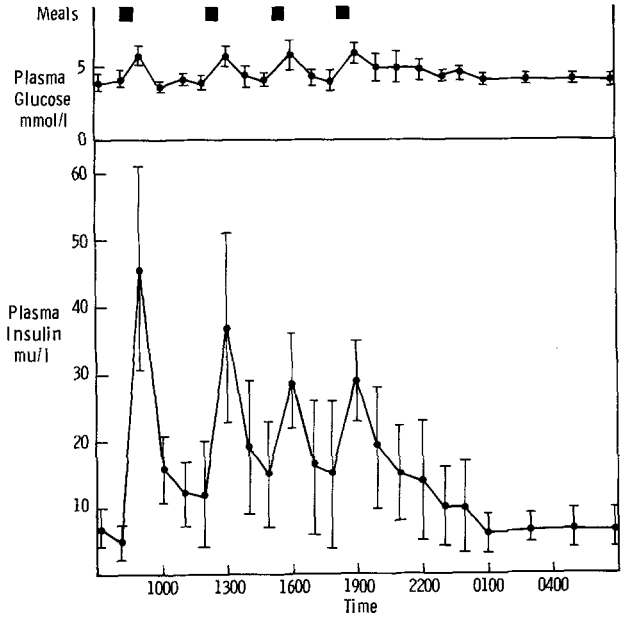

Fig. 4. Plasma glucose and insulin levels (mean ± ISD) in eight normal men from data of Holman and Turner (see Text)

longer than the other groups but show a higher incidence of blindness.

It is, however, important to get this into proper perspective because without insulin all would have died within two or three years of diagnosis. Reference to Figure 2 will show that many are alive and well twenty or thirty years after the diagnosis of diabetes and the start of insulin injection therapy.

Insulin Therapy in Insulin Deficient Diabetics

To try to improve the long-term prognosis for the insulin deficient diabetic, it is relevant to examine the circulating insulin pattern in the normal subject and to compare it with that achieved with insulin injections in insulin deficient diabetics. At the same time it is accepted that the insulin profile in peripheral venous blood gives little indication of the insulin content of portal vein blood to which the liver of a non-diabetic is exposed.

Glucose and insulin profiles in eight normal men are shown in Figure 4. This is drawn from data obtained by Dr. R. R. Holman and Dr. R. C. Turner of the Radcliffe Infirmary, Oxford [14]. The peak shown one hour after each meal is the mean of the highest level found after the meal in samples taken at 10 minute intervals. The highest level occurred any time between 20 and 60 minutes after the start of the meal. In contrast the serum insulin level after a subcutaneous injection rises much more slowly and, provided no insulin antibodies are present, reaches a peak about 150 minutes after the injection (Fig. 5). During the day it might be possible to achieve a pattern resembling the insulin concentrations in the peripheral blood by giving soluble insulin three times a day. To avoid hypoglycaemia, however, it would be necessary to use slowly absorbed carbohydrate, possibly with additional dietary fibre [15] and to give additional carbohydrate between meals.

The problem of ensuring an adequate serum insulin concentration during the night hours necessitates the use of longer acting insulin. For reasons of expediency many physicians use a mixture of rapidly acting and an intermediate acting insulin in the morning and evening. This reduces the number of injections to two a day and hopefully provides reasonable blood glucose levels. The most commonly used intermediate acting insulin is isophane insulin. Figure 6 shows the free-insulin level in a diabetic patient who had two injections of soluble insulin during the day and soluble and isophane insulin in the evening. The free insulin was measured by the polyethylene glycol precipitation method of Nakagawa et al. [16]. The levels during the night were too high, there was subclinical hypoglycaemia detected by serial measurements of blood sugar. It might be argued that this could easily be corrected with a smaller dose of isophane insulin, but with this preparation, it is difficult to find a dose that will avoid nocturnal hypoglycaemia but control

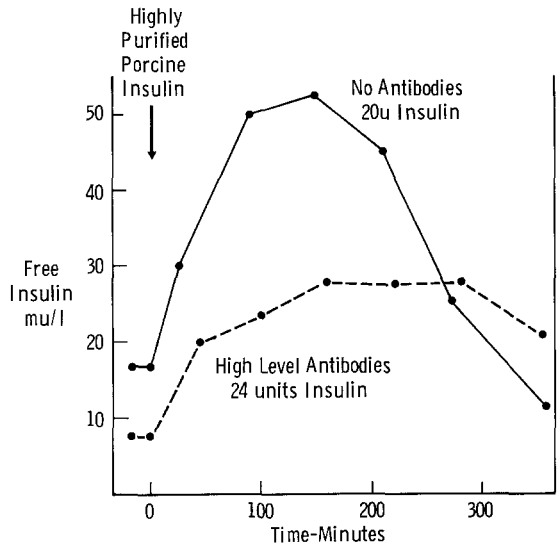

Fig. 5. Free insulin concentration in two insulin deficient diabetics. One without antibodies given 20 units highly purified porcine soluble insulin, the other with a high level of antibodies given 24 units of insulin

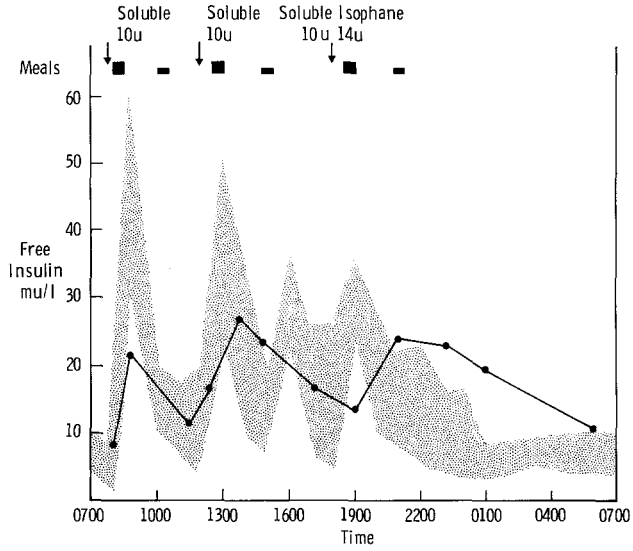

Fig. 6. Free insulin concentrations with three doses of soluble insulin and isophane insulin before supper. The shaded area is the mean ± ISD of the normal subjects shown in Figure 4

blood glucose up to the time of the next injection. As an alternative to isophane insulin in the evening, we are now studying the effect of an insulin zinc suspension (Lente-Monotard) and this may produce a satisfactory night time pattern. We have not found it easy to control patients on two injections of quick-acting and lente insulin and we are now studying a regime with quick-acting and isophane insulins in the morning and quick-acting and lente insulin in the evening (Fig. 7).

The effect of insulin antibodies on the diurnal insulin pattern of insulin treated diabetics is considerable. Figure 5 shows the free insulin levels after an injection of quick-acting insulin in two diabetics, one without insulin antibodies and one with antibodies. It is clear that with a high level of antibodies it will be very difficult to achieve a physiological peak of free insulin concentration. The level of antibodies developed varies greatly from patient to patient, and we have, at present, no means of detecting which patient will develop antibodies. It seems advisable to start all newly diagnosed insulin deficient diabetics on a highly purified insulin, which, although it does not prevent antibody formation completely, seems to keep it at a much lower level. This limits the type of insulin preparation that can be used to Actrapid MC or Leo Neutral insulins for quick action; Leo Retard as an isophane insulin and Monotard MC which may have a longer action. Semitard MC is available as an intermediate acting insulin, but carries greater risk of nocturnal hypoglycaemia.

In the last year, we have been studying blood

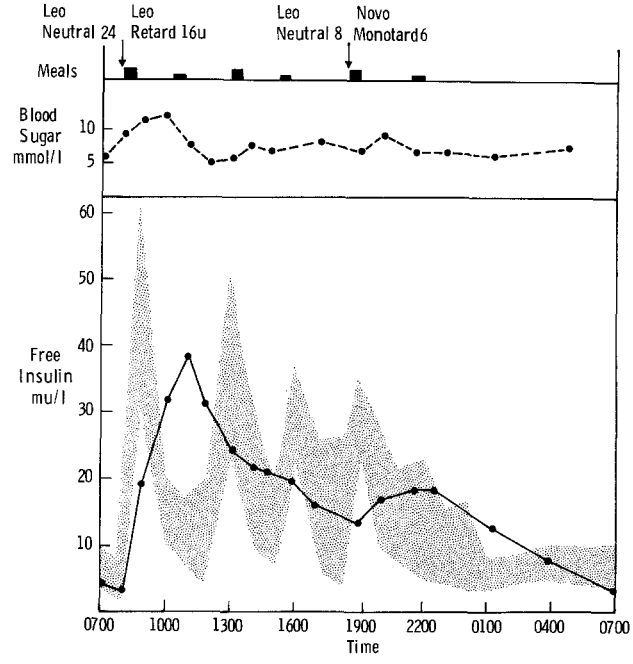

Fig. 7. Blood glucose and free insulin profile in a patient having highly purified soluble and isophane insulin before breakfast and soluble and lente insulin before supper. Shaded area as in Figure 6

sugar and free insulin profiles partly in our own unit and partly in conjunction with Dr. R. B. Tattersall and Dr. E. A. M. Gale in Nottingham. Three points have emerged from these studies. The first and probably the most important is the occurrence of asymptomatic hypoglycaemia during the night. This is gen-

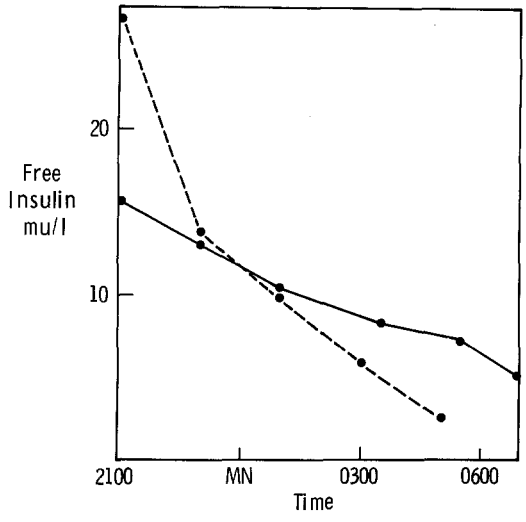

Fig. 8. Free insulin levels in the same patient after 12 units of isophane insulin before supper (Patient of Drs. R. B. Tattersall and E. A. M. Gale, Nottingham)

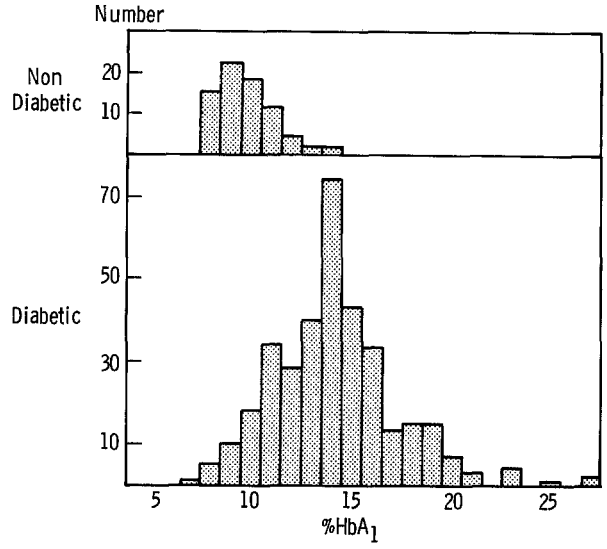

Fig. 10. HbA1 in 72 non-diabetic and 348 diabetic patients

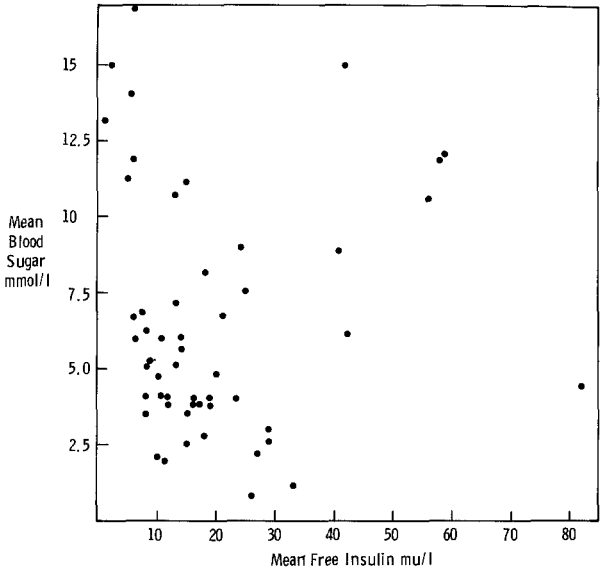

Fig. 9. Relationship between mean blood glucose and mean free insulin between midnight and 0800 h. 53 studies on 33 patients. On the right of the figure are 7 studies on 5 patients with unexplained resistance to a high free insulin level

erally accepted as being a common occurrence with Semilente insulin given before supper. We have been surprised to discover how often it occurs with isophane insulin given before the evening meal. We have also encountered it with Monotard insulin in a dose as small as 12 units. Probably the most important outcome of our studies has been the realisation of the need to check blood sugars in the early hours of the morning if diabetic control is proving difficult. The second point that has emerged has been the variation of the rate of absorption of insulin. There obviously must be some variation and in long standing diabetics with fibrosis in most of the possible injection sites this may become a serious problem. Figure 8 shows the free insulin levels in a patient following an injection of 12 units of isophane insulin. On one occassion absorption was rapid and on the other much slower. The third point is that some diabetics are apparently resistant to surprisingly high levels of free insulin. This is illustrated in Figure 9 where the mean free insulin and blood sugar levels between midnight and 0800 h are shown in 53 studies on 33 patients. With mean free insulin below 35 mU/l there is the expected relationship with the association of a low free insulin and a high blood sugar or a high free insulin and hypoglycaemia. However, there are 7 studies on 5 patients who had high free insulins with hyperglycaemia or, in one case, normoglycaemia. These patients were not obese, diabetic control was difficult to achieve and we do not know the reason for their insulin resistance.

Monitoring Diabetic Control

It is well recognised that single blood sugar measurements in a clinic are a very poor indication of overall diabetic control. Serial measurements taken in hospital are artificial and rarely satisfactory. There is no doubt that home self-monitoring with one of the currently available 'stick' reading machines offers the possibility of greatly improved diabetic control and increases the patient's understanding of his or her disease [17, 18]. In our experience very frequent

measurements are not really necessary and we ask the patient to check blood glucose four times a day – not every day – but periodically. This may be of particular value in establishing the levels of blood glucose in the early hours of the morning.

The other important development in the monitoring of diabetic control is the use of a simple method for measuring the glycosylated haemoglobins [19]. Using the method described by Welch and Boucher [20], we have measured the levels of HbA1 a+b+c in 72 control non-diabetic subjects and 348 patients from our diabetic clinic. The results are shown in Figure 10. They give little ground for complacency, and we have not found the high correlation between clinical assessment of control and blood sugar levels v. HbA1 described by Gonen and Rubenstein [19]. We have, however, noted the gradual fall in level when a new diabetic is treated and a rising level or unexpectedly high level in a treated patient is a warning that something is going wrong.

The Future

Currently available insulin preparations could be better used to treat patients with diabetes. We should be using the purest insulins probably of porcine origin. The best results would probably be obtained with a rapidly acting insulin before breakfast and before lunch, with before the evening meal a rapidly acting highly purified insulin with a small dose of a longer acting insulin. If three injections a day were not acceptable to the patient the morning injection might be quick-acting with an intermediate acting insulin. The dose would be adjusted by the patient on the results of his own blood sugar measurements and the long-term assessment of control made by the Diabetic Clinic using HbA1 measurements.

In the future a truly miniature implantable or portable artificial pancreas seems a long way ahead. Pancreatic or islet cell transplantation also seems to be a very remote possibility. Even if rejection problems could be overcome, the difficulties in obtaining donor material seem insuperable. Metered insulin infusion may provide better control without any feed-back based on blood sugar levels. Intravenous infusion seems too hazardous for continuous use, but developments are in hand with subcutaneous infusion [21]. The possibility of intraperitoneal infusion is worth further study because at least part of the insulin is likely to enter the portal venous drainage system [22]. Clearly we have a great deal still to do to realise the full potential of Banting and Best's great discovery.

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