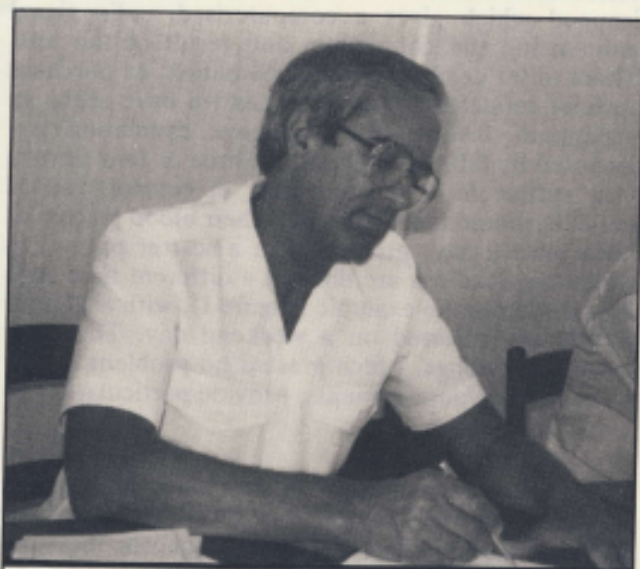


Diabetes today — a review and update (Part II)



Curriculum Vitae

Dr Robertson studied at Cape Town University where he received the MB ChB in 1954. He did some post-graduate training at Mc Cord Zulu Hospital (Durban) and St Monica's Home (Cape Town), received the MFGP (SA) in 1975 and has been in Private Family Practice in Durban since 1957. He has a wide interest in different fields of medicine, and at the moment still holds the following posts: Senior Medical Officer – Diabetes Dept (Addington Hospital), Medical Director – Child Guidance & Research Centre (Durban/Westville), Medical Director – Institute of Human Sexuality. He also makes time to serve on several committees. He is Vice-chairman of the council of SA Academy of Family Practice/Primary Care; he is an elected member of the SA Medical and Dental Council and gives time to many other committees serving the community. Dr Robertson has presented many papers at Medical Conferences, has published several scientific papers and contributed to two medical textbooks. He is married to Barbara and they have 4 children.

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KEYWORDS: Diabetes Mellitus; Glucose Tolerance Test; Insulin; Hypoglycemia; Self Medication; Self Assessment

Summary

A practical approach to the understanding of diabetes mellitus, its terminology, diagnosis and etiology as well as clear guidelines for the management of the diabetic patient in general practice.

IN 1869 a German medical student, Paul Langerhans, announced in his dissertation that the pancreas contained two systems of cells, and that, apart from the acini, there were also other cells floating like islets in a sea of acinar cells – islets which now bear his name. It was another twenty years before Minkowsky discovered in 1889 that depancreatized dogs developed polyuria and glycosuria. Some thirty odd years were to pass before those intrepid Toronto workers made their first crude extracts of pancreas until, in 1923, Banting and MacLeod were awarded the Nobel Prize. Another twenty five years later came the first observation of long-term complications and it was thirty years after insulin was first used to treat diabetics before Keiding and his co-workers suggested that control of diabetes

would be useful in preventing vascular complications.¹

And still we blundered on preaching the gospel “keep the urine green” – which suggested that a little glycosuria protected against hypoglycaemia. Is it cynical to wonder whether the glycosuria also meant fewer problems for the diabetic's physician? At any rate, microvascular complications continued unabated. In the mid-1970's came a giant step for diabetic mankind when Jean Pirart, in his monumental prospective study of 4 400 diabetics showed that microvascular complications were clearly specifically related to the degree of glycaemic control.^{2, 3}

Sadly, in 1986 there are still many who continue to espouse the “keep it green” philosophy.

Diabetes today — a review and update

With Pirart's work came also the realisation that the use of urine-testing for glucose was not adequately sensitive for satisfactory control.⁴ Not only did glucose only start to spill into the urine when blood levels reached twice normal, but the renal threshold for glucose changed the longer the disease continued. Even in young diabetics one often finds negative urines in the presence of blood glucose levels of up to 14 mmol/l.

Self-monitoring of blood glucose represented the next big advance, and while this initially involved the use of reagent strips, the first of which were not very accurate, the introduction of reflectance meters using the same strips made really reliable Home Blood Glucose Monitoring (HBGM) a feasible proposition.

Home blood glucose monitoring

Home blood glucose monitoring is now one of the mainsprings of diabetic management and is particularly useful in the detection of nocturnal hypoglycaemia, a common cause of problems in the insulin treated diabetic. It also enables the patient to proceed towards the goal of education in which the diabetic becomes his own doctor. Home blood glucose monitoring did, however, have the disadvantage that the results could not be checked by the attending physician and was therefore dependent on the patient's truthfulness. Fortunately, since 1976, a method became available whereby the accuracy of HBGM could be verified, namely the HbA1c or glycosylated haemoglobin.⁵ Three reflectance meters are available in the RSA, namely

- the Glucometer which uses Dextrostix strips (Ames),
- the Reflolux which uses Haemoglukotest strips (Boehringer-Mannheim), and
- Glucocheck II which also uses Haemoglukotest strips.

Samples for the home blood glucose monitoring estimations are taken from fingerpricks, and spring-loaded blood letting devices which are relatively painless such as the Autolet (Ames) and the Autoclix (Boehringer-Mannheim) have greatly increased the acceptability of HBGM. A recent innovation is a reflectance meter suitable for the visually handicapped which gives a computerised audio signal announcing the countdown and result of the test. There is no need for a NIDDM patient to purchase such of reflectance meter for, as we have seen, an occasional fasting blood glucose estimation augmented by HbA1c estimations three or four times a year suffice for the monitoring of control. IDDM patients should ideally monitor their blood glucose at least once a day, preferably in a scatter pattern in which the readings are done at a different time each day as seen in the example (Figure 1), with a 24 hour profile as indicated on a weekend day. The early morning readings, which present no problem for my disco-loving young patients, provide particularly valuable information.

Before considering the other main primary or idiopathic type of diabetes, Type I or IDDM, it may be useful to discuss a few additional diagnostic measures and indices other than the blood glucose and OGTT (which we discussed in part one and are of value in diagnostically defining the diabetic state). These additional indices are useful in defining subclasses of diabetes, and in epidemiological studies help to determine the mechanisms and natural history of diabetes.⁶

These indices fall into two categories:

1. Indices of the diabetic process

These currently include the characterisation of HLA types and subtypes; the presence, type and titre of circulating antibodies directed against the pancreatic islets; evidence of pancreatic or other endocrine disease

Date	before breakfast	2 hours after breakfast	before lunch	2 hours after lunch	before supper	2 to 3 hours after supper	between 3 and 4.30 a.m.	Doses and comments
30/3/86								
Monday	5,6							MONOTARD HbA1c 8 ALTRAPID HbA1c 3
Tuesday		8,9						
Wednesday			7,2			(3,1)		GYM 5-6 AM BIGGER SNACK 10 AM
Thursday				6,8				
Friday					5,4			
Saturday	4,9	9,2	8,8	7,4	5,0	8,1	5,1	LAZY DAY GARDENING
Sunday								

Figure 1. Scatter Home Blood Glucose Monitoring for IDDM

Note: Once control is established the number of tests may be reduced. For example, alternate tests may be done on weekend days and the early morning tests on alternate Saturdays/Sundays only.

and evidence of cell-mediated immunity directed against the pancreas.

2. Indices of the degree of beta-cell damage

These include measurements of insulin, pro-insulin and connecting peptide (C-peptide) secretion. Perhaps the most valuable in terms of assisting the monitoring of the quality of diabetic control are values of HbA1c, or the degree of the glycosylation of other proteins.

This is not a complete list, and time will certainly see the number of these additional tests increase. The only one which merits a full discussion for the purposes of this review is the HbA1c.

The HbA1c

The HbA1c (synonyms: glycosylated haemoglobin or glycated haemoglobin or glucated haemoglobin) is a stable product of a non-enzymatic reaction between glucose and haemoglobin. The product resulting from this reaction is formed slowly and irreversibly throughout the 120-day lifespan of a red cell. The higher the average circulating blood glucose the higher the HbA1c, and we can therefore use the test as a measure of long term glycaemic control in the diabetic, as opposed to the blood glucose estimation, which only reflects the situation at the moment of drawing the sample. Several methods are available for the measurement including chromatographic techniques, colorimetric methods and electrophoretic separation.

Why use the HbA1c?

(1) The most important use for the test is to monitor diabetic control in both IDDM and NIDDM patients. Glycosylated haemoglobin provides a more accurate picture of the metabolic control over the previous eight to ten weeks. In IDDM patients it provides a useful measure of the accuracy of HBGM programs, and in this situation should be performed every two months. As already indicated, in NIDDM patients a fasting blood glucose every one to two months should be supplemented with an HbA1c every four to six months.

(2) Whilst the test lacks the sensitivity of the raised blood glucose or OGTT in the diagnosis of diabetes it could be a useful adjunct, particularly as it does not require the patient to fast. Its main value in this regard, however, is to detect the increasing number of patients who, prior to having blood glucose tests or OGTTs for insurance purposes surreptitiously take oral hypoglycaemic drugs to mask their hyperglycaemic state. The same applies to the many patients who tighten up control with diet and oral hypoglycaemics a few days before their appointments.

(3) The test is of particular value during pregnancy.

The HbA1c is of no value in monitoring short term control or assisting in the determination of insulin doses. As with any laboratory test the HbA1c is not infallible and can under certain circumstances give misleading results:

- (1) Haemolytic conditions may give low readings.
- (2) After splenectomy high readings may occur.
- (3) Uraemia. A combination of haemolytic and chemical factors have the net result of lowering the anticipated HbA1c.
- (4) High doses of aspirin give falsely high levels due to acetylation of haemoglobin.
- (5) Iron deficiency results in longer red cell life and falsely high HbA1c levels.
- (6) Certain abnormal haemoglobins such as HbS and HbF may also influence the results of the test.

The last three conditions have effects on the HbA1c which are method-dependant, as they may or may not affect the results depending on which laboratory method is used.

Type I diabetes mellitus — IDDM

Diabetics who require exogenous insulin comprise a far smaller group than those who do not. Though, as in the case of NIDDM, no race is immune, there are nevertheless certain groups in which the disorder is rare or virtually unknown. The highest rates occur in Caucasian populations. Various studies of the prevalence of IDDM indicate an incidence per 100 000 children which ranges from 7 in Japan to 223 in Scandinavian countries.⁷ Comparisons should be made with caution, however, because slightly different age-groups were studied and the methods of case assessment also varied. Accepting these reservations, there are undoubtedly vast geographic and ethnic differences, much as applies in NIDDM. The incidence and prevalence of IDDM are high by international standards in all Nordic countries, and Finland has the highest incidence and prevalence figures for the disease in the world, with a mean annual incidence of 28.6 per 100 000 in the 0 to 14 year age group, a prevalence of 191.⁸ Furthermore, children in the United States of America are about 20 times more likely to develop IDDM than children in Japan.⁹ The reasons for these differences will be examined when discussing the aetiology of IDDM. There have not been any epidemiological studies of the disease in our various groups but in children one has an impression that IDDM is commonest in our white population and indigenous blacks but uncommon in the South Africans of Indian origin, whilst coloured children occupy a position somewhere between the white and the black populations. It should be mentioned that where children are concerned there is seldom any doubt about the diagnosis of IDDM in that they are, in the main, C-peptide negative and truly exogenous insulin dependent.

Where older persons are concerned the actual diagnosis is sometimes in doubt, and these patients may exist for long periods without exogenous insulin, indicating that they have some residual islet function. However, more about this 'grey zone' in a later section.

The sexes are equally affected. There are definite age peaks in the incidence with one of particular magnitude occurring at 10 to 13 years of age. Some limited data also suggests a rising trend in some countries.

Aetiological and risk factors

Certainly in Europeans, possession of the HLA-Dw3/DR3 and/or HLA-Dw4/DR4 alleles of the major histocompatibility complex on the short arm of the 6th chromosome is a marker of susceptibility to IDDM whilst, conversely, the possession of HLA-Dw2/DR2 appears to be protective against the disease. Other

Not infrequently there is a history of physical or psychological trauma before the onset of severe hyperglycaemia.

alleles with which IDDM is associated are HLA-B8 and HLA-B15. Furthermore, HLA-identical siblings of probands with IDDM are at extremely high risk of developing IDDM themselves.¹⁰ It is interesting to speculate that there may be a higher incidence of the main 'risk' antigens (DR3/DR4) or a lower incidence of the 'protective' DR2 in Scandinavia or the United States of America or other countries with a high incidence of IDDM. This has not been borne out by surveys, however, so other factors must be responsible for the discrepancies. Also, concordance rates for IDDM in identical twins are only about 50 per cent, which is far lower than the 100 per cent one would expect if only genetic factors were determinants of the disease. There must, therefore, as we have noted in the case of NIDDM, be other factors which precipitate the disease in genetically susceptible individuals.

There are indeed some environmental factors which seem to fill such a rôle. These include certain toxic substances such as streptozotocin and alloxan, as well as a rodenticide, pyrinuron, the ingestion of which has produced diabetic keto-acidosis. The intake, by pregnant women, of certain nitrosamines in foods, for example in smoked and cured mutton, has been implicated as a cause of IDDM in the offspring.

Epidemiological studies provide strong circumstantial evidence for a possible causative rôle of viral infections

in IDDM. Amongst the viruses which have been implicated are rubella, mumps and human coxsackievirus B4. There are clues which hint that IDDM may be caused by an altered immune reaction against antigens present in the beta cells of the islets and/or in the environment. Most recently diagnosed patients show both cellular and humoral auto immunity against beta cells. An appealing hypothesis is that the combination of specific Class II antigen molecules coded by HLA genes such as DR plus an invading antigen (which may be viral, bacterial or chemical) challenge

Not infrequently young children have a history of enuresis after having been dry for some time.

the immune system and trigger the formation of effector cells such as B lymphocytes and cytotoxic T lymphocytes which crossreact with beta cells. Repeated attacks of this nature over a period of years eventually destroy sufficient islet beta cells to create a need for exogenous insulin.

Our ability to detect Islet Cell Cytoplasmic antibodies (ICA) and Islet Cell Surface antibodies (ICSA) has advanced our knowledge of the autoimmune nature of this complex disorder. That the process of islet-cell destruction will have continued for many years before the disease is clinically manifest is indicated by the presence of ICA for a period of two to seven years before the diagnosis of IDDM.

Clinical presentation

The vast majority of Type I patients presents with the classical triad of polyuria, polydipsia and loss of mass, accompanied by hyperglycaemia, glycosuria and ketonuria. Young children not infrequently have a history of enuresis after having been 'dry' for some time. The degree of hyperglycaemia is generally such that the diagnosis is not in doubt so that there is no need to perform an OGTT, which could, in fact, be very dangerous. In those cases which are not diagnosed early the patient may present in ketoacidotic coma.

As previously noted, though the onset is usually abrupt, the destruction of islet beta cells will have been going on for a period of up to some years earlier as evidenced by the presence of ICA. Not infrequently there is a history of physical or psychological trauma, or viral or bacterial infection just before the onset of severe hyperglycaemia.

After the abrupt onset, the natural history of the disease is often characterised by an apparent remission, the so-called "honeymoon" period, during which improved beta cell function (and also increased beta cell mass) is demonstrable. This may last several months, but eventually residual beta cell function again goes into progressive decline some six to nine months after the diagnosis of the diabetes. Complications of the eye, kidney and nervous system may occur, usually after many years of the disease. Survival depends on the provision of daily injections of insulin. It used to be said that diabetics have a shortened lifespan compared with non diabetics, but this needs to be challenged in the light of improvements in the types and quality of insulins available and the newer methods of monitoring and managing disease.

Management of IDDM

Once over the initial period of ketoacidosis, the management of which will be discussed in a later section, the management of the Type I patient is much more straightforward than the average family practitioner realises. It is my opinion that the almost religious adherence to the credo of the 'sliding scale' has hampered the understanding of diabetes by practitioners and the early control of their diabetic patients. Consider the theory on which the sliding scale is based, which holds that by doing a 24 hour blood glucose profile and then giving short-acting insulin at intervals (of 4 to 6 hours) we can eventually work out the required dose of insulin by adding up the total dose of short-acting insulin and converting this into a combination of short- and intermediate-

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So far so good! But what is more likely to happen in practice is that the desired euglycaemia is seldom achieved for longer than a short time, and instead we find rapid excursions from underground to ceiling blood levels of glucose, with the decisions as to the insulin dosage required always made *post hoc*, so that the total dose of short-acting insulin bears no relationship to the ultimate dose of the combined insulins necessary for good control. And there are many otherwise reputable institutions where sliding scales based on urinary sugars are still used.

The widespread belief that diabetics have a shortened lifespan needs to be challenged.

The sliding scale should be allowed to slide into oblivion!

Now, just as dosages for all pharmacological agents can be worked out using ranges based on body mass, so too can the required dose of insulin — and with a surprising degree of accuracy. The dosage range is between 0,6 and 1,1 international units of insulin per kilogram of body mass per 24 hours. As the patient will invariably be hospitalised at this stage, it is my own practice to start with doses based on the higher levels of this range. Any hypoglycaemic episodes can be speedily dealt with and, indeed, if they do occur they constitute a very useful part of the patient's educative process as he gains insight into a condition that he will have to live with and deal with for the rest of his life.

The standard method of deploying the total dose arrived at by this method is to split it into two doses, with two thirds given 30 minutes before breakfast and the remaining third given 30 minutes before supper. Each of these doses is split into two thirds of intermediate-acting and one third of short-acting insulin. Take for example the case of an IDDM patient with a mass of 75 kilograms:

0,6 to 1,1 i.u. X 75 kg = 45 i.u. to 82 i.u. of insulin daily.

Using the 0,6 international units per kilogram dose the total daily dose is divided into 30 international units (2/3rds) before breakfast, which is given as two thirds in the form of intermediate-acting insulin (20 i.u.) and one third as short-acting insulin (10 i.u.). Similarly, the 15 international units of insulin given before supper is divided into 10 international units of intermediate-acting and 5 international units of short-acting. If basal blood glucose levels are high or post-breakfast levels

consistently above 10 mmol/l it is useful to split the evening doses and give the short-acting insulin before supper and the larger dose of intermediate-acting insulin at bedtime.

It is not possible, using exogenous insulin, to achieve physiological insulin profiles as we are constrained by —

- (1) the abnormal route of administration (i.e. subcutaneous),
- (2) the insulins available, and
- (3) the lack of continuous control of insulin delivery by blood glucose levels.

Classification of insulin preparations

This can cause confusion as insulins can be classified on the basis of *purity* (e.g. 'P.I.F.' or pro-insulin-free, or 'M.C.' or monocomponent); by *formulation* (e.g. Isophane, or lente); by *species* (e.g. beef, pork or 'human'); or by *duration of action* (e.g. short-, intermediate- or long-acting). Strength is no longer a problem in this country, as only U100 (or 100 i.u. per cc) insulin is available. Our therapeutic choice is usually based on duration of action (see Figure II).

Short-acting preparations are true solutions of insulin ('Soluble insulin') and can be administered subcutaneously, intravenously, intramuscularly or intraperitoneally. These are the only insulins used in Continuous Insulin Infusion Pumps (CSII). Isophane insulin is prepared by fixing insulin-molecules to fish protamine, a virtually non-immunogenic foreign protein. It can only be used subcutaneously. Lente insulin is complexed with zinc to lengthen its duration of action. Such solutions contain free zinc which combines with soluble insulin when the two are mixed, thus blunting the onset of action of the latter. Protamine zinc insulin has insulin complexed with both fish protamine and zinc.

All complexed insulins are cloudy, settle on standing and must be inverted to mix before using.

Species of insulin

Beef insulin differs from human insulin in three amino acid residues, while pork is more similar to the human variety in that it has only one amino acid substitution. Human insulin can now be made from pork insulin by substitution of the correct amino acid or by recombinant DNA techniques in which the human insulin gene is inserted into a bacterial host (*E coli*).

The insulins obtained by these two methods are identical in action, and there is increasing evidence that the use of human insulins offers advantages both in reduced antigenicity¹¹ as well as improved metabolic control¹². In one recent double-blind study human insulin was significantly less immunogenic than either purified pork or mixed beef/pork insulin.¹³

Choice of insulin regime

In the non-diabetic insulin output is at a low basal level throughout the night and rises sharply within 5 to 10 minutes after each meal, and then reaches a peak at 45 minutes before returning to basal levels after 2 hours (Figure III). During exercise insulin secretion is suppressed. To get perfect metabolic control in the diabetic this has to be imitated, a virtual impossibility because—

- (1) after subcutaneous injection of soluble insulin plasma concentrations rise slowly, peak at 75 minutes, then fall slowly, halving approximately hourly;
- (2) intermediate-acting insulins peak at 5 hours and then also decline, halving every 6 hours; and
- (3) exercise increases insulin absorption.

Ultralente preparations, being slowly absorbed, promise more stable basal concentrations, but, unfortunately most preparations do so erratically and with poor or unpredictable bio-availability.

Figure II Classification of insulins by duration of action

Short acting	Acid soluble Neutral soluble
Intermediate acting	Isophane Lente
Long acting	Ultralente P.Z.I.

Once daily injection regimes are suitable only for Type II patients who require exogenous insulin but have considerable endogenous insulin reserves. The twice daily injection regimes using mixtures of short- and intermediate-acting insulins as already discussed, are suitable for most IDDM patients, but the plasma insulin profile (Figure III) is far from physiological, with late morning hyper-insulinaemia and gross hyper-insulinaemia after midnight but insulinopaenia at dawn. Splitting the doses with the short-acting before supper and intermediate at bedtime may solve the morning hyperglycaemic problem.

We have recently had excellent results with the use of a regime in which a new and as yet unavailable ultralente preparation with a flat basal delivery ('Ultratard HM Novo') was given once in 24 hours at about 22h30, combined with three pre-prandial injections of a short-acting insulin. The fact that four injections were necessary did not appear to pose problems for the twenty patients involved, possibly because the short-acting insulin was delivered with a pen-injector device ('Novopen') which did not cause much pain and which in addition offer convenience of transport.

The ratios of total daily insulin used were

- 40 % as "Ultratard HM" given at 22h30
- 25 % as "Actrapid HM" given before breakfast
- 15 % as "Actrapid HM" given before lunch
- 20 % as "Actrapid HM" given before supper

Two tremendous advantages obtained with this method were that hypoglycaemic episodes were reduced to a minimum and that these patients enjoyed a freedom from the strict meal regimens which usually apply to the average diabetic. This new-found flexibility meant that snacks between meals could often be omitted, and meals could be taken at convenient times, such as supper after returning from an early show.

All IDDM patients should use some form of home blood glucose monitor.

It should be noted that the basic principle underlying this method can be reproduced using ordinary insulin syringes and one of the freely available intermediate-acting insulins as the basal delivery insulin.

For further information on the various insulin regimes which may be used in different situations the reader is referred to the useful free booklet for general practitioners *Practical guidelines for the management of diabetes*.¹⁴

Dosage can be worked out on body mass.

All IDDM patients should use some form of HBGM whether this is by visual assessment of strips such as 'Visidex II' (Ames), 'Haemoglukotest 20-800' (Boehringer-Mannheim), or with the aid of one of the reflectance meters. The results so obtained forms the basis on which alterations are made in the insulin doses by the patient under the tutelage of the doctor or nurse-diabetologist. Most of the errors which are made in these dosage adjustments arise when alterations are made ad hoc from day to day. This usually results in wild swings from very low to compensatory high levels as the counter-regulatory hormones go into action to try to restore glucose homeostasis. Hence the following guidelines for any dosage adjustments:

Guidelines for dosage adjustments

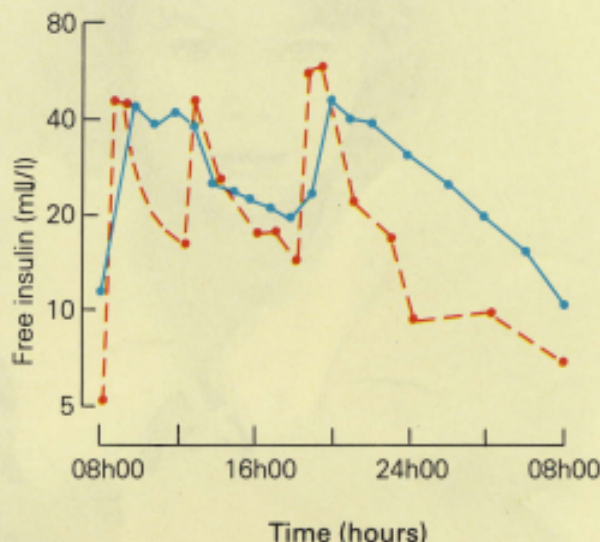
- (1) Before taking action against abnormally high or low glucose at any time, first ensure it is not a 'one off' situation but a pattern, by testing at the same time for another two days.
- (2) Then try and determine what is responsible for the unusual level, for example, too big a snack, too much exercise or the preceding dose of insulin. Thus, a high blood sugar at 16h00 on a b.d. regime would, in the absence of dietary indiscretions, indicate that the morning intermediate insulin needs increasing. All adjustments in insulin doses should be made 2 international units at a time.
- (3) Guard against simultaneously making adjustments to both diet and insulin, or to diet, insulin and exercise.

A not infrequent dilemma arises when blood sugars are persistently high on rising, and then continue high after increasing the night dose of the intermediate-acting insulin. This may be due to the patient having undetected hypoglycaemic excursions after midnight, with an over-enthusiastic counterregulatory response which carries the blood sugar above the normal range on rising and after breakfast. Hence the previously pointed out need to test in the small hours of the morning on occasion, say 02h00 to 04h00.

Although medication (in the form of exogenous insulin) plays a far more prominent rôle in the total management of IDDM than medication (in the form of oral hypoglycaemic agents) does in the management of NIDDM, it should be emphasised that no form of insulin therapy will be successful without adequate blood glucose monitoring, attention to diet and adequate and appropriate exercise.

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Plasma free insulin profiles in non-diabetics (red) and IDDM patients on B.D. short/intermediate insulin regime (08h00 and 18h00) (blue). Note the rapid rise and fall of physiological insulin levels with each meal, and the slower rise and fall with subcutaneous insulin. Also note the hyperinsulinaemia in the late morning and around midnight in the diabetic profile.

Figure III. Free insulin profiles in IDDM patients on a B.D. mixture of short and intermediate insulins

(Adapted from Philip Home in *Medicine International*, April 1985.)