

## Increased Insulin Requirements in Diabetes Mellitus

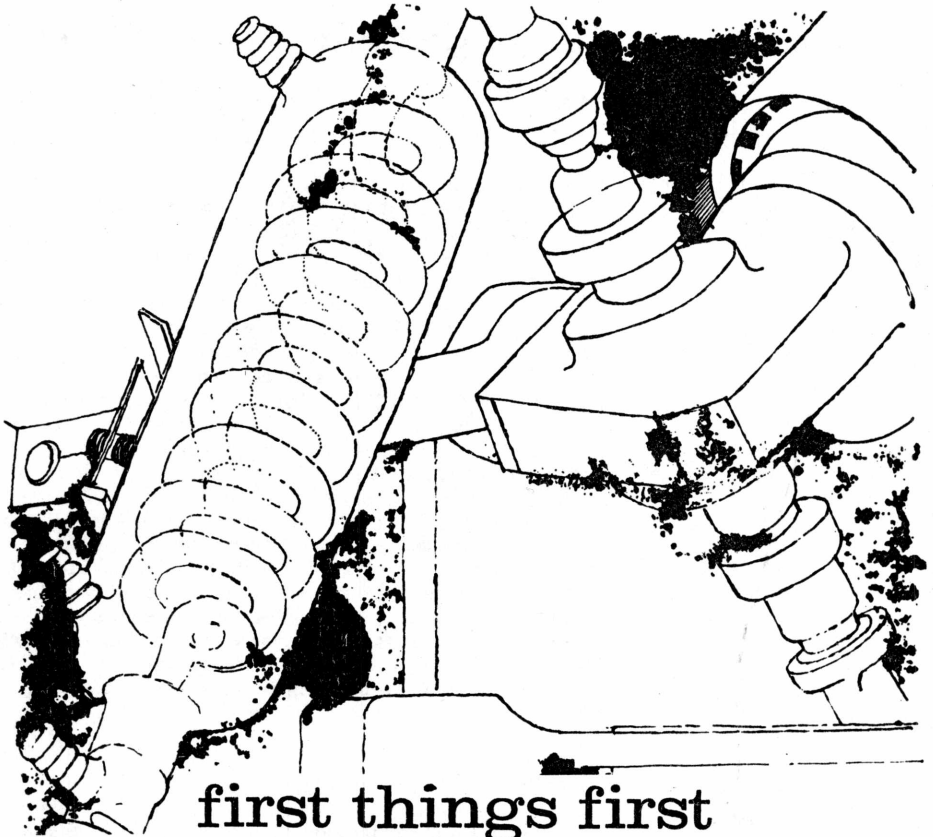
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Diabetes Mellitus remains one of the most fascinating entities in medicine which, in spite of a great deal of research and investigation, remains an enigma with the basic aetiology(s) still unknown. The pathological and clinical findings have been well documented and the therapy has been described by many authors, each expressing his own opinion as to the best management of a diabetic patient. It is well known that the therapy of patients with Diabetes Mellitus resolves around diet, exercise, proper education and finally use of insulin. Generally speaking, it is not particularly difficult to outline a program of treatment for a diabetic patient, but such an outline does not necessarily result in good control. One of the more interesting problems in the management of a diabetic patient is the occurrence of increasing insensitivity to insulin with the result that the physician frequently prescribes ever increasing amounts of insulin in an attempt to control the glycosuria and hyperglycaemia with varying success. In some cases the patient may suffer severe fluctuations in blood sugar, resulting in hypoglycaemic symptoms which may alternate with hyperglycaemic episodes and evidence of ketonaemia and ketonuria. The increased insulin requirements in children and adults with Diabetes Mellitus may be due to many causes that the physician must be aware of if he is adequately to manage such patients. The definition of "insulin resistance" varies with the interpretation of the physician in relationship to the amounts of insulin prescribed. It is suggested that amounts of insulin above 50 units a day in children and above 200 units a day in adults may be interpreted as "insulin resistance". However, these values are perhaps somewhat rigid and one must take into consideration the age of the patient, the rapidity of onset of increased insulin requirements and the severity of the symptoms in deciding whether the patient is truly insulin resistant.

### THE MECHANISM OF INSULIN ACTION:

The mechanism of insulin action has been investigated for many years with many theories and suggestions, but as yet the essential and fundamental action of insulin remains unknown. It is generally agreed, however, by most investigators that insulin primarily facilitates the conversion of extracellular glucose to intracellular glucose 6-phosphate. It was suggested at one time that insulin directly altered the hexokinase activity in the presence of inhibitory pituitary-adrenal components. However, it was subsequently shown by Levine et al (1) that the action of insulin is directly on the cell membrane or wall in which the entry of glucose into the cell is facilitated. More recent investigation would suggest that insulin has a dual action which results in (a) increased penetration of glucose into the cell and (b) in correcting a decreased intracellular phosphorylating mechanism in the diabetic state. The effect on permeability is immediate while the effect on phosphorylation is somewhat slower and is sensitive to pituitary and adrenal factors. This dual role of insulin is a difficult one to understand unless phosphorylating and penetrating mechanisms have several components in common. Certain other effects are extremely important and frequently less well known. These include effects on fatty acid synthesis from acetate in the liver; the effect on hepatic glycogen synthesis; effect on amino acid composition and incorporation to protein and effect on hepatic glucose release. More recently it has been suggested that skeletal muscle insulin primarily affects the electric membrane potentials in ionic concentration gradients.

It is also necessary to be familiar with the variation in sensitivity to insulin by certain body tissues; for instance adipose tissue may be more sensitive to smaller concentration of insulin and to smaller changes in insulin concentration than many other tissues as recorded by in vitro assays. It is of interest that certain tissues such as brain are not affected by the presence or absence of insulin.



## first things first

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**INSULIN REQUIREMENT:**

The amount of insulin required by an individual may be affected by many factors. These include:

- (A) the rate of secretion of insulin by the Islets of Langerhans;
- (B) the rate of insulin utilization;
- (C) the rate of insulin degradation.

Very little is known with regard to the rate of secretion as well as the rate of insulin utilization. It is not known if insulin is degraded while exerting its action or whether it must continue to be present in "active" form after it has initiated certain reactions. With regard to the rate of degradation it is known that Thyroxine or Triiodothyronine in rats increases insulin degradation and in the hypothyroid state insulin degradation is reduced.

**CAUSES OF INCREASING INSULIN REQUIREMENTS IN DIABETIC PATIENTS:**

A diabetic patient who has shown poor control for some time with increasing insulin requirements should stimulate the physician to think of several possibilities.

(1) Associated Disease:

Infection is likely the chief cause of poor diabetic control and increasing insulin requirements. Such infections not uncommonly are associated with staphylococci infections in the skin or infections of the teeth, sinuses or lungs. Pulmonary tuberculosis must be watched for particularly in adolescent diabetes. One of the most difficult infections to diagnose involves the genito-urinary tract. It is imperative that careful examination of a centrifuged specimen of urine be carried out by the physician looking for pus cells and granular or white blood cell casts with a routine urine culture also being carried out. It is interesting to note the significant reduction in insulin requirement when a previously unsuspected urinary infection is brought under control by the appropriate antibiotics following urine culture. Such patients may have been erroneously considered as truly "insulin resistant" with some temporary improvement with increased insulin dosage, but not until control of the urinary infection is established will a significant reduction in insulin and control of the diabetes be accomplished. A second major disease resulting in increased insulin requirement is the presence of malignancy or carcinoma. It is well known that in diabetic patients who develop leukemia a marked increase in insulin dosage will frequently occur.

(2) Emotional Disturbances:

It is now well recognized that various emotional upsets will result in loss of good control in Diabetes Mellitus. Frequently in adolescents who develop a problem with regard to management the cause may be improper emotional adjustment to the disease during the adolescent period. In general, however, the increased demands for insulin are not as great in comparison to other causes, but nevertheless are sufficient to result in poor diabetic control and great fluctuations in blood sugar resulting in the administration of increased amounts of insulin.

(3) Hormonal Increase or Imbalance:

The chief hormones involved with abnormalities in carbohydrate metabolism include epinephrine, glucagon, glucosteroids, growth hormone and thyroxine. It is well known that in patients with acromegaly and Diabetes Mellitus there is a great increase in the requirement of insulin for diabetic control. This is in part due to increased production of growth hormone and thyroxine. The exogenous administration of glucocorticoids is well known to increase the requirement of insulin. It is therefore important that the physician be aware of the various hormonal influences and in the patient presenting with poor diabetic control consideration must be given to exclude various endocrine gland abnormalities.

One might comment at this time on juvenile diabetes and the increased requirement of insulin during the adolescent period. It is not uncommon for insulin requirement in the adolescent diabetic to increase rather markedly after ten or eleven years of age with a fall in insulin requirement at seventeen or eighteen

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years. This seems to be related to the rapid increase in growth and development, and likely has some relationship to growth hormone, thyroxine and gonadotrophin secretion.

Hyperadrenal corticism must also be considered in an insulin resistant patient. It has been shown that the majority of patients with diabetes and acromegaly show insulin resistance and that hyperthyroidism and Cushing's syndrome are associated with insensitivity to insulin control.

(4) Insulin Antagonists and Circulating Antibodies:

During the past ten years there have been increasing reports in the literature of insulin insensitivity due to interference with insulin action by serum insulin antagonists or to the binding of insulin by circulating antibodies (2) (3). Vallance-Owen (4) has described the presence of insulin-antagonist material that appears to be bound to albumin. This investigator has described an antagonistic factor to insulin in serum which is bound to the albumin fraction and is present in diabetics and normal individuals, but much less active in the latter. This material is counteracted by some other substance, possibly insulin.

Loveless and Cann (5) have described blocking antibodies in the gamma globulin fraction of serum proteins which neutralize or bind insulin and are associated with insulin resistance. Berson and Yalow (3) have shown that although the total binding capacity was the same, the ratio of bound to free insulin was markedly less when the sera from some diabetic patients treated with beef-pork insulin were tested with pork insulin than that obtained when tested with beef insulin. This binding of insulin by blocking antibodies apparently is reversible. With regard to the production of insulin antibodies it has been suggested that this may be species specific. Lowell (2) described a patient who responded to human insulin while resistant to beef insulin. This suggested species specific antibodies present in some cases. It may be stated here that the local skin reaction to insulin injection in which erythema and slight swelling may occur along with some discomfort is due to antibodies of the "reagin" type. This "allergic" reaction probably plays no important role in insulin resistance.

(5) End-organ Refractiveness:

The possibility of refractiveness of the cells to insulin has been of interest to many investigators but at the moment such an explanation of insulin resistance is not suggested by good scientific evidence. Field described a patient who required 38,000 units a day of insulin for three months. This patient had a plasma insulin titre 4,000 times the normal value. There was no plasma antagonist demonstrated and it was found that the half-life of Insulin 1131 in plasma was somewhat increased, which suggested the possibility of some deficiency in certain body cell constituents resulting in refractiveness to normal or increased amounts of insulin. The possibility exists that growth hormone may, in some cases, produce a change in tissue cells which results in refractiveness to insulin or that growth hormone may produce insulin antagonistic material in plasma.

TREATMENT OF INSULIN RESISTANCE:

Management of a patient with increasing insulin requirements involves a detailed and careful history and similarly a very careful physical examination. It is essential that the physician exclude infection as the underlying cause of the patient's poor diabetic control. It is not uncommon for some diabetic patients to show increased glycosuria a few days prior to the development of a cellulitis or skin infections or symptoms of an abscessed tooth. Careful assessment for pulmonary tuberculosis should be made in all adolescent diabetics.

Brief comment should be made regarding the problem of "paradoxical hyperglycaemia." In this situation the patient shows initially some slight glucose intolerance with increased glycosuria. This in turn results in the patient increasing their dosage of insulin, but the glycosuria instead of improving tends to increase. Over the next several days to two weeks the dosage of insulin is progressively increased, but in spite of this the patient shows no evidence of coming under control. It is of interest that in some such cases a reduction of 30% to 50% in the insulin dosage will result in significant im-



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provement in the hyperglycaemia and glycosuria. Such cases have been described as "paradoxical hyperglycaemia" in which the increased insulin produces a fall in blood sugar which is compensated by an increase in adrenal-cortical activity. Thus great swings in the blood sugar occur and instead of progressive improvement in control of the diabetes with increased insulin administration the patient becomes worse and the swings in hyperglycaemia increase and it is not until the physician appreciates the possibility that too much insulin is being administered that improvement results. Treatment in these cases is relatively simple in that careful assessment of the diet and a reduction of insulin result in significant improvement.

Introduction of the oral hypoglycaemic agents in 1955 resulted in a new and interesting development in the management of diabetes. In some patients with apparent insulin resistance the administration of oral hypoglycaemic agents may result in significant improvement and a decrease in the amount of insulin required. Nabarro (6) described the use of Tolbutamide in the management of brittle diabetics in 1960. Other investigators have not been impressed with the value of this form of therapy.

Steroid therapy has been used in some patients with increasing insulin requirements with apparent favourable results. The theory is that the steroids result in interference with the binding of insulin by antibodies and both Corticotrophin and Prednisone have been used. It has been found that there may be a significant fall in insulin requirement, but this requirement increases when the steroids are discontinued. Oakley et al (7) has shown a dramatic fall in insulin requirements following Prednisone therapy in four patients in whom insulin antibodies were detected by a reversed passive cutaneous anaphylaxis technique.

One of the more interesting aspects is that which was described by Lowell in 1944 (2) who presented two cases of insulin resistance due to neutralizing antibodies. One of the patients responded to human insulin while resistant to beef-pork insulin. Pork insulin has been used successfully by French and Dutch workers and more recently a case was described in a child by Goldman (8). The difference in chemical structure of beef insulin from that of pork insulin resides in three amino acids within the disulphide ring of the A-chain. In beef insulin the amino acids alanine, serine and valine are present, whereas in pig insulin there is a structural change with a substitution of threonine, serine and isoleucine. It has been suggested that there is a ten-fold difference in antibody binding which is probably due to this particular structural difference. These insulins have been used to assess their effectiveness with the result that in some cases of severe insulin resistance pork insulin may be used. The most commonly available insulin preparation is a combination of beef and pork insulin, usually 70% beef and 30% pork. It has been shown that insulin binding globulins are present in the circulation of human subjects treated with commonly available beef-pork insulin preparation. These anti-bodies have been shown to bind pure beef insulin seven to ten times more actively than pork insulin. Pork insulin has been provided by the Eli Lilly Co. for the treatment of cases of insulin resistance with some suggested success (8).

More recently a new insulin has been produced by the Connaught Laboratories in Toronto under the direction of Dr. P.J. Maloney. This insulin is a beef insulin that is especially processed in sulphuric acid to produce a sulphated or sulphonated insulin which appears to have beneficial effect in patients with increased insulin requirement due to insulin resistance or circulating antibodies. Nine patients have been treated at the Children's Hospital with favourable results. Two of the patients were considered as insulin resistant in which greater than 200 units of insulin per day were required for reasonable control. A marked reduction in insulin requirement occurred when sulphated insulin was used and would indicate that this insulin may have a valuable place in the treatment of patients with insulin resistance.