Current Practice

CLINICAL PROGRESS

Diabetes: Underlying Biochemical Lesions

K. W. TAYLOR, PH.D., M.B., B.CHIR. *

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The discovery 50 years ago that injections of insulin would restore many diabetics to normal health naturally prompted the idea that diabetes was usually due to insulin deficiency. While in one sense this view is still the correct one, it has had to undergo some considerable modification. For example, the insulin deficiency may be relative rather than absolute owing to insulin antagonism (as is seen in obese diabetics). Again, in many diabetics the insulin secretion is only a little less than normal, but secretion is delayed following a glucose stimulus. These ideas have aroused considerable interest in the biochemical control of insulin secretion. Knowledge of these processes has recently very greatly expanded, owing to the introduction of methods to study isolated islets of Langerhans, in which insulin is made and secreted.^{16 17}

Normal Regulation of Secretion

Insulin is released by discharge of granules containing the hormone in a crystalline stored form.¹⁸ The level of glucose reaching the beta cells of the islets of Langerhans is normally the most important factor determining the rate of insulin secretion by this process. Studies using isolated islet cell preparations have shown that glucose is normally metabolized by the islets to induce secretion. Normally, secretion of insulin does not begin until the levels of glucose reach 5 mM in the fluid reaching the islets.^{19 20} This corresponds with a blood glucose level of 90 mg./100 ml. Above this level of glucose, insulin secretion rises linearly with increasing glucose concentration. There are clearly many ways in which the rates of secretion could be influenced by modifying the metabolism of the β cell. For example, the rates of phosphorylation—the initial stage in glucose metabolism—could be affected. Alternatively, the amount of glucose flowing through one of the several routes, such as the pentose phosphate pathway known to be important in secretion, could be altered.

Secretion Due to Other Substances

Very many substances are now known to be able to influence insulin secretion, though apart from amino acids (and in some animals, such as ruminants, short chain fatty acids), few appear to be important physiologically. The sulphonylureas (which include such substances as tolbutamide or chlorpropamide) are the most important group of substances which promote insulin release. Their mode of action is unknown. Often substances such as glucagon or corticotropin increase insulin secretion by activation of the intracellular messenger substance, cyclic 3' 5' adenosine monophosphate—

important in many other secretory processes.²¹ It is far from clear, however, whether all forms of insulin secretion are mediated through cyclic AMP.

Insulin synthesis is now believed to proceed through a single polypeptide chain precursor, proinsulin, from which the double chain hormone insulin is later split off by the action of a trypsin-like enzyme.²²

Inhibition of Secretion

The drug diazoxide, which was first used in the treatment of hypertension, directly inhibits secretion of insulin due to glucose. It has been used with some success in the treatment of hypoglycaemia. Adrenaline is also a potent inhibitor of insulin release in animals or in man.²³ The effect is probably the major precipitating factor in the diabetes which is associated with pheochromocytoma.

Diabetes Due to Insulin Deficiency

Some diabetics present with symptoms of acute insulin deficiency at the onset of their disease, which in all essentials resembles that which accompanies destruction of the islets by chemical agents such as alloxan. The acute insulin deficiency results in the familiar pattern of hyperglycaemia, rapidly progressive ketosis, and loss of body protein. Both alloxan and a more recently discovered beta cell cytotoxin, streptozotocin, may induce a diabetic state when used for the treatment of islet cell tumours, but so far no comparable chemical agent has been shown to induce spontaneous diabetes in man. The lack of insulin in this type of diabetic has been repeatedly confirmed by plasma insulin estimations using a wide variety of methods.²⁴ The alpha cells of the islets, which make and secrete glucagon, are much less affected, and serum glucagon levels may be relatively high in insulin deficient diabetics.²⁵

If acute diabetes of this type is not due to some toxic factor it may possibly sometimes be associated with an autoimmune process, or be the result of a viral attack which affects the beta cells. The possibility that some cases of acute diabetes in the young follow a viral infection has recently been discussed in detail, though the problem is far from settled.^{26 27}

Diabetes Associated with Obesity

Many earlier studies in which insulin levels in blood were measured suggested that maturity onset diabetics secreted a sufficiency of insulin. It was assumed that in these patients hyperglycaemia was due to defective insulin action rather

* Reader in Biochemistry, University of Sussex.

than to insulin deficiency. This view does not now seem to be a correct one. When the blood glucose is raised in such patients there may be an excessive secretion of insulin. Nevertheless, these levels are still less than those observable in normal people, in whom the blood glucose is raised to comparable heights.²⁸ In addition, the secretion of insulin in such patients may show a delay.

These patients show insulin antagonism, which seems to be directly associated with their obesity; thus insulin is less effective in non-diabetic obese subjects than in normal people. Similarly, animals made experimentally obese may show a resistance to the action of insulin.^{29, 30} The non-diabetic obese person is, however, able to compensate for this insulin resistance by secreting extra insulin; in the mild diabetic adequate compensation does not seem possible, presumably because of some β cell defect.

The nature of the insulin antagonism that accompanies obesity is the subject of dispute. Both circulating antagonists,³¹ as well as a tissue antagonism based on a deranged fatty acid metabolism,³² have been postulated to account for it. Carbohydrate restriction leading to weight reduction may restore both glucose tolerance and insulin secretion virtually to normal in these patients, emphasizing that in the absence of obesity the β cells of such patients may function adequately.

Other Hormones and the Islets of Langerhans

Both growth hormone and the structurally similar material derived from the placenta, placental lactogen, appear to affect the islets of Langerhans. In man diabetes quite commonly accompanies acromegaly. Excess growth hormone has long been known to induce diabetes in some animals,³³ partly through a direct effect on the islets and partly by increasing resistance to insulin. Nevertheless, smaller quantities of growth hormone may raise blood insulin, probably by a direct effect on the β cells. This effect which takes some hours to develop may involve a sensitization of the islets to the secre-

tory effects of glucose.³⁴ Growth hormone also affects the β cells themselves directly to increase insulin synthesis. The extra responsiveness of the β cells may be especially important during growth, since insulin is important in increasing protein synthesis at this time.

Similar changes may occur during pregnancy, probably as a result of the secretion of the hormone placental lactogen, which closely resembles growth hormone in structure and properties. The effects of this substance may underly the increased insulin secretion which is known to accompany pregnancy. The alterations in metabolism in pregnancy may produce a temporary diabetic state—gestational diabetes, which disappears after delivery.

Insulin Secretion in Potential Diabetes

In the nomenclature of the British Diabetic Association the term potential diabetic is restricted to those who are particularly liable to develop diabetes. Ideally this category includes the identical twins of a known diabetic. As a group, unaffected identical twins of diabetics secrete less insulin in response to glucose than do normal people, either as a result of an intravenous glucose tolerance test³⁵ or after oral glucose,³⁶ though there may be considerable individual variation.³⁷ The delay in insulin secretion in this group may be due to the ineffectiveness of a system involving cyclic AMP, which promotes insulin release.

In summary, diabetes is often associated with some defect within the β cell, leading to an impairment of insulin secretion. This may range from complete β cell destruction to relatively minor changes in secretory response. Factors such as obesity or pregnancy in which there is an increased need for insulin may accentuate the abnormality. The discovery of a low insulin response to glucose among close relatives of diabetics emphasizes the possibility of inherited defects in the secretory mechanism for insulin. It is, however, much too early to be certain of their true significance in the aetiology of most cases of clinical diabetes.

General Treatment of Diabetes

D. A. PYKE,* M.D., F.R.C.P.

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In a month or two it will be 50 years since Banting and Best started their work leading to the discovery of insulin. It seemed then that the problem of treatment of diabetes had been solved; it has dawned on us gradually over the years that it has not. Indeed, not only have advances in treatment been slow, there is now even a suggestion that a well-tried oral agent—tolbutamide—might be harmful (the evidence presented to the American Diabetes Association on 14 June³⁸—but not yet published in a medical journal—that patients on tolbutamide show an increased late incidence of arterial disease will need to be carefully scrutinized).

New Insulins

Recently two new types of insulin³⁹ have been introduced. The first is a neutral soluble insulin (Nuso in the United Kingdom, Actrapid in Denmark). Ordinary soluble insulin is

strongly acid and when mixed with neutral insulins produces a change in pH which affects, to a variable degree, the time-effect of the insulin mixture. It has therefore been unsatisfactory to mix soluble with the lente insulins, but it is now possible in those patients on lente insulin who show day-time hyperglycaemia and glycosuria and night-time hypoglycaemia to mix Nuso or Actrapid with lente and often obtain good control. The presumed advantage of Nuso and Actrapid that, being neutral, they are more quickly absorbed, is not of practical significance.

The second new type, "biphasic" (Rapitard) insulin consists of a mixture of neutral soluble and Crystal II insulin. It was hoped that this insulin might provide effective 24-hour control of blood sugar with a single injection. In practice this is seldom the case and usually biphasic insulin has to be given twice daily. Actrapid insulin, being pork insulin, is useful in the rare cases of species insulin resistance.

In spite of these new insulins there has recently been little real change in insulin therapy. Indeed, there has been a turning back to two-injection regimens (soluble insulin alone, or

* Physician, King's College Hospital, London S.E.5.