SOME CLINICAL ASPECTS OF DIABETES WITH RELATION TO INSULIN AND TOLBUTAMIDE

A DISCURSIVE SURVEY WHICH ASKS SOME QUESTIONS BUT ANSWERS NONE*

W. P. U. JACKSON, M.A., M.D., M.R.C.P., D.C.H.,

Diabetic Clinic, Department of Medicine, Groote Schuur Hospital and University of Cape Town

A. VARIETIES OF DIABETES

I should like to start by reaffirming the clinical separation of diabetes mellitus into 3 types, severe, mild, and secondary. 'Severe' refers to the usually young, growth-onset, ketosis-prone individual, who needs insulin to live. 'Mild' refers to the usually older, maturity-onset, often obese person, who does not become ketotic when insulin is omitted, although he (or more usually she) may be relatively insensitive to insulin and require 100 or even more units to produce any obvious effect on her carbohydrate metabolism. The dose of insulin being used is no criterion of the severity of the diabetes. Severe and mild diabetes are sometimes called 'pancreatic' and 'extrapancreatic' respectively, on the assumption that the disease in the first case is due to destruction of pancreatic beta-cells, and in the second to anti-insulin factors which may or may not be hormonal. However, insulin antagonists have been found in the blood-stream of the severe diabetic rather than in the mild case, while islet-cell damage probably always occurs in the pancreas of the mild diabetic, in whom both Ogilvie[1] and Gepts[2] have found an invariable reduction in amount of islet tissue. Vallance-Owen[3] has shown that the insulin-like activity in the blood-stream of the mild diabetic is of the same order as in a fasting normal person. This, however, does not mean that the pancreatic activity is normal; far from it, since an induced rise of blood sugar in the normal to the height of that in the mild diabetic produces a several-fold increase in plasma-insulin activity. Thus the mild diabetic possesses a pancreas which is unable to respond normally to the stimulus of a raised glucose level.

It may be noted that the terms 'mild' and 'severe' refer only to the evidence of abnormality of metabolism; both types may develop the same crippling or killing vascular complications, both may present similar inheritance patterns and occur together in the same family, and both may give evidence of their latent existence by the same sort of abnormal obstetric history and embryopathy in the prediabetic phase. It is also true that a mild diabetic may develop ketosis under the influence of certain forms of stress, while occasionally a severe diabetic reverts to the mild form. I have twice seen patients in hospital in diabetic coma, without any known precipitating factors, who were normoglycaemic some months later without insulin. Nevertheless the clinical differentiation of the main primary types of diabetes is extremely important and remarkably often neglected. For instance, figures concerning the clinical use of sulphonylureas with regard to age of patient, insulin dosage and so on are quite useless unless the two diabetic groups have first been clearly separated.

'Secondary' diabetes refers most obviously to that which follows chronic destructive pancreatitis, haemochromatosis or total pancreatectomy. The diabetes which occurs during pregnancy, staphylococcal infections or acromegaly, or with moderate doses of glucocorticoids, is not truly secondary, but rather the unmasking of an underlying latent or pre-diabetic state. Fig. 1 shows a corticoid diabetic (European male aged 35, suffering from gout) becoming apparently normal after cessation of treatment, but again diabetic—this time permanently—a few months later.

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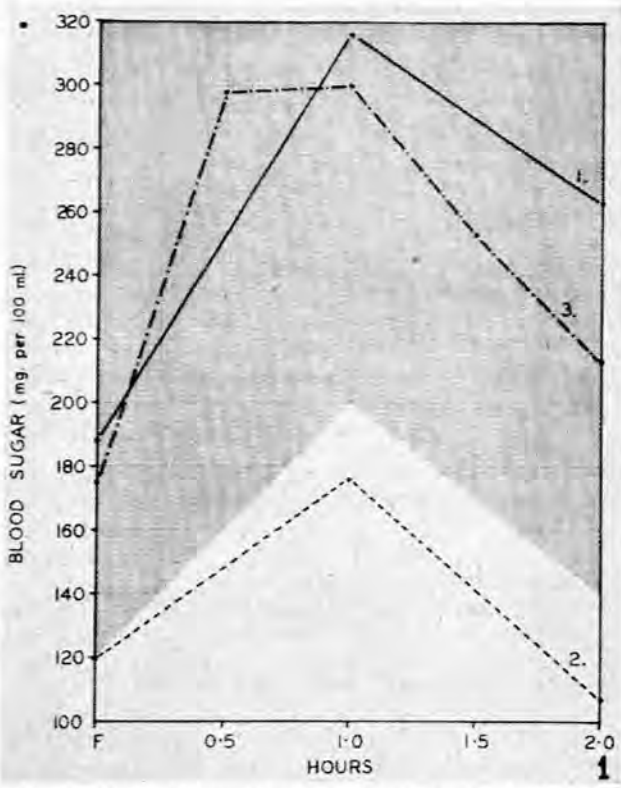

Fig. 1. 'True' diabetes uncovered by cortisone. 1. Diabetic after 4 months on cortisone. 2. Normal curve off cortisone. 3. Eight months later, no more cortisone: again diabetic. (Glucose-tolerance curves using 50 g. of glucose by mouth.)

PREDIABETES AND VASCULAR DISEASE

Many of us believe that, strictly speaking, diabetes begins at birth, that the basic abnormality, whatever it may be, is present for the whole of the lifetime of the diabetic, although the overt carbohydrate defect may not be manifest until middle age. Time precludes discussion of the arguments in favour of this belief, beyond my remarking that the elderly diabetic who attends your clinic may give a history of large babies and stillbirths which extends back 30, 40 or 50 years into her prediabetic past. Furthermore we consider that the specific vascular abnormalities of diabetes are not 'complications' but are an integral part of the syndrome, inherited together with the metabolic disturbances. Usually they appear later than the hyperglycaemia, but sometimes before it. They are not a consequence of hyperglycaemia, and normalization of the latter, even in the very mildest cases, is no safeguard against their occurrence. It would, however, appear that they are closely connected with pancreatic damage, since true secondary pancreatic diabetes has occasionally led to the later development of specific retinopathy or nephropathy.

These various observations are extremely important, since they appear to intimate that a defect of pancreatic islet tissue may produce a diabetic vasculopathy which is not dependent upon hyperglycaemia. Indeed we have perhaps been overobsessed with hyperglycaemia as the primary feature of diabetes. Insulin has an action in fat metabolism which may well be more important than its more obvious effect on carbohydrate. It is closely related to the level of the non-esterified fatty acids, and stimulates rapid metabolism in fatty tissue. It has now been shown to exert an influence on amino-acid metabolism.[4] Might it perhaps have an essential protective effect on blood-vessel walls? A future diabetic might be born with a relatively inefficient beta-cell mechanism, not so defective that our rough yardsticks of definition based on glucose tolerance can detect it, but bad enough that throughout the years certain blood vessels in certain places become progressively damaged. The special stress of pregnancy may indicate the latent deficiency by producing temporary carbohydrate intolerance in the mother, death or excessive size of the foetus, and hyperplasia of the foetal islets of Langerhans.

INSULIN AND PREDIABETES

This hyperplasia of the islets of Langerhans in the foetus of a diabetic or a prediabetic mother is a remarkable phenomenon. Table I shows the relative proportions of islet tissue to the

TABLE I. PROPORTIONS OF ISLET TISSUE IN PANCREASES IN DIFFERENT GROUPS (EXPRESSED AS MEAN PERCENTAGES OF TOTAL PANCREAS)

Control stillbirths	1·3%
Stillbirths of diabetic mothers	6·5%
Stillbirths of prediabetic mothers ..	7·5%
Stillborn with erythroblastosis foetalis ..	7·1%

whole pancreas which Woolf and I[5] found on examination of 108 pancreases from stillborn infants. Fig. 2 illustrates a pancreas from the foetus of a prediabetic mother (B) compared to a normal at the same magnification (A). From the small amount of suitable material available to us, it seems that not only are the islets large and increased in number, but they contain an unusually high proportion of beta cells, and these beta cells contain an unusually great concentration of granules. If granules really represent insulin, then it would appear that the pancreas of such a foetus may contain up to 30 times as much insulin as normal. What could be the cause of this beta-cell hyperplasia? It is not hyperglycaemia, because it occurs in the absence of hyperglycaemia in the prediabetic. Growth hormone and glucocorticoids have been much discussed in connection with the diabetic embryopathy, but there are cogent arguments against either of these as the sole or primary villain of the piece. Might not the maternal lack of pancreatic reserve during pregnancy militate through some mechanism other than hyperglycaemia to allow a compensatory hypertrophy of the infant's islets? Now the excessive insulin produced by the infant might itself act as a 'growth hormone' in its own intra-uterine development. Could this possibly account for the excessive size of the diabetic's baby?

If this story has any truth, then insulin might be expected to prevent the diabetic vascular abnormalities, the foetal and obstetric abnormalities, and possibly the actual development of overt diabetes in a prediabetic. Certainly, and unfortunately, insulin will not prevent all vascular disease in diabetics, but there is much evidence that when it is given in such a way that good control of glucose metabolism is achieved then the liability to vascular lesions is, in general, considerably lessened. Figures from our own clinic indicate that the incidence of retinopathy and neuropathy in poorly controlled diabetics was double that in diabetics whose control was good or excellent. Now if our belief regarding

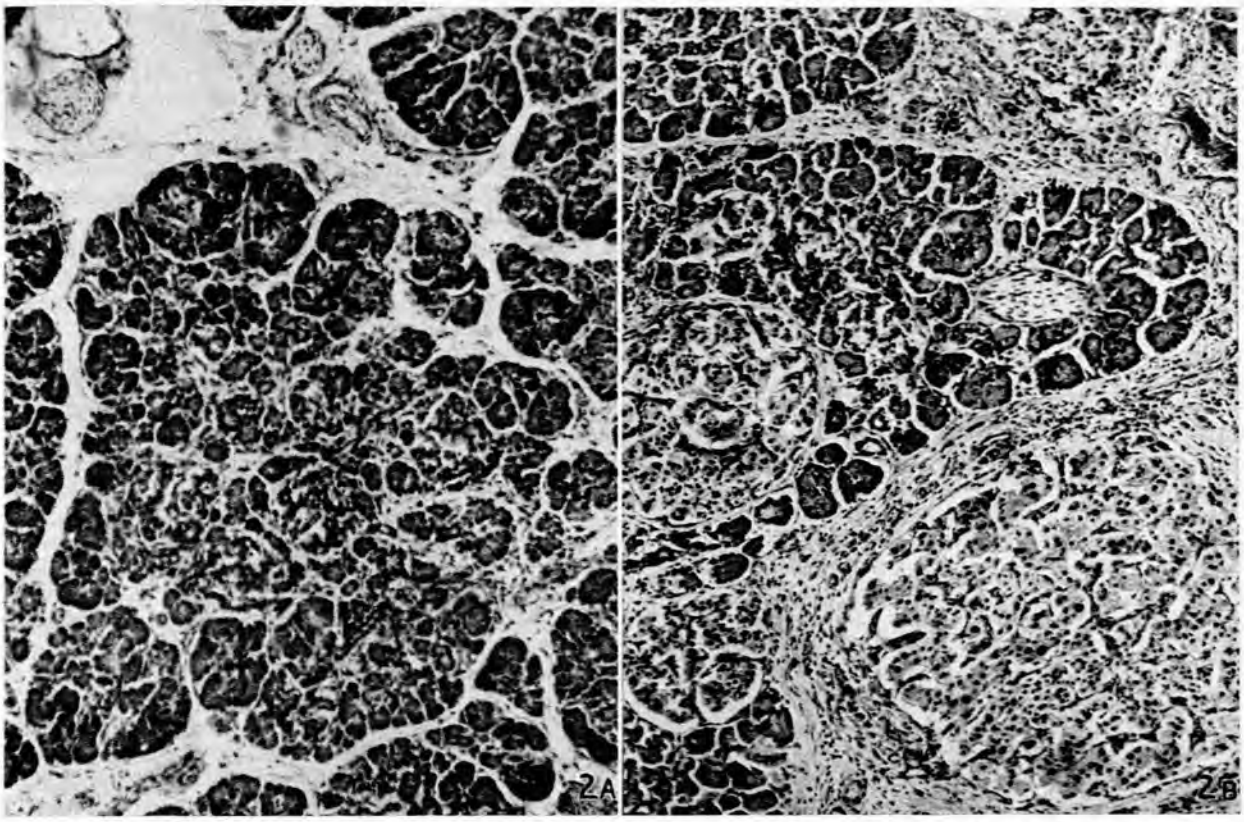

Fig. 2*A*. Photomicrograph of pancreas of stillborn of normal mother. *Fig.* 2*B*. Photomicrograph of pancreas of stillborn of prediabetic mother.

the presence of diabetes from birth is true, it is surely plain that insulin given only when overt carbohydrate defects are present would not be expected to prevent a lesion which has already been developing for a long time. If we could give insulin early in the prediabetic phase, might we not then prevent the vascular disease? This, of course, is not known, but it is worth considering. Methods used in diagnosing prediabetes I will not consider here, but it may be mentioned that certain family histories make a diagnosis of pre- or latent diabetes mandatory; for instance when both parents are diabetic, when an identical twin is diabetic, or in such a family as is shown in Fig. 3. Prof. Hoet[6] has indeed some evidence that insulin given to a prediabetic woman during pregnancy will prevent the development of severe congenital abnormalities, while Wilkerson[7] from Boston has shown that the same treatment will tend to reduce the birth weight of the foetus. Further, Hoet[5] has pointed out that the child of a known diabetic mother being treated with insulin seldom becomes diabetic under the age of 10, whereas almost all mothers of children who become diabetic under the age of 6 are untreated latent or pre-diabetics. Insulin given during pregnancy may thus have a protective action on the child. Is it just possible that insulin given to children in diabetic families would prevent diabetes entirely? It protects the pancreas of animals against alloxan.

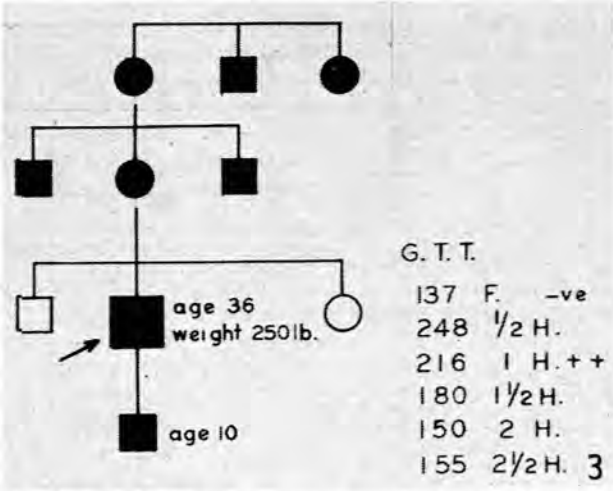

Fig. 3. The blacked-in figures represent diabetics. The proband (arrowed) had a diabetic son, mother, and grandmother. There was no diabetes on his wife's side. He did not know he was diabetic, but the family history led to his having a glucose tolerance test; result as given.

PROPHYLAXIS WITH INSULIN OR ORAL SULPHONYLUREAS

It is admittedly impracticable to suggest that babies or even adults should be stuck with a needle every day without a great deal more evidence of its value. Could the oral sulphonylureas take the place of insulin in prophylaxis? It is very important that we should know the mode of action of these substances before embarking on such a programme. If their

major action is a stimulation of beta cells with the production of insulin, then there are two ways in which their use in prophylaxis would differ from that of insulin. First it might be presumed to overtax the already inefficient beta cells, rather than to rest them. The whole idea of continued stimulation producing permanent structural damage to the beta cells is, however, rather nebulous, has been too readily accepted, and finds no proven counterpart in the rest of the endocrine system, nor indeed in other organs of the body. Gepts,[2] furthermore, has found that the damage to islet cells in elderly patients treated with carbutamide or tolbutamide is no greater than that seen in a group of similar untreated or insulin-treated diabetics, while in some he found actual regeneration of apparently active beta cells. The second difference between tolbutamide and *exogenous* insulin is that the *endogenous* insulin which is formed under the influence of tolbutamide would be liberated into the portal system, and so might really act more physiologically than insulin injected peripherally. Thus Madison and Unger[8] have shown that insulin administered intraportally in dogs produces a much smaller arterio-venous glucose difference than when systematically introduced, suggesting a lesser effect on muscle and probably a greater hepatic effect. Tolbutamide does not appear to be toxic in other ways—in fact it seems to be about the most non-toxic drug ever produced. Theoretically it might appear inadvisable to give it to a prediabetic or diabetic during pregnancy, since we have evidence that the beta cells of the foetus are already being excessively stimulated. Although tolbutamide might be called simply a drug of convenience in the treatment of the established mild diabetic, it may yet be of true value if used early enough, especially in the prediabetic.

The advent of the antidiabetic sulphonamides has taught us more about diabetes as seen in the clinic. In the trial of carbutamide and tolbutamide which we carried out, we made it a rule to withhold all insulin from our mild diabetics for several weeks before starting the new drug, in order to obtain a proper control base-line. We were surprised to find the number of patients whose carbohydrate metabolism was as well controlled on diet only as it had been with insulin also. In fact in a few the control was actually better without insulin. This has led to a considerable reduction in the number of patients taking insulin in our clinic. Furthermore it clearly indicates that any trial of an oral preparation in diabetes is valueless without periods during which no drug at all is taken. Although insulin was apparently being given unnecessarily to the above-mentioned patients, yet perusal of their previous records frequently indicated that it had been prescribed to good purpose when originally administered, 2, 3, or 5 years before. This might be interpreted in 2 ways; either the disease in its natural course had become milder or, as I prefer to think, the insulin had really had a partially curative effect.

Some clinics in Britain have been strongly advocating a return to the use of soluble insulin alone for the control of all severe, insulin-dependent diabetics. They claim not only better carbohydrate control, but also a greater protection against vascular disease than is afforded by long-acting insulins. I do not consider they have proved either point, and it must be remembered that the long-acting insulins were introduced largely because 2 injections of soluble a day were inefficient in diabetic control. We have found, after some 5 years experience, that the lente group of insulins are generally satisfactory and we consider that their wholesale abandonment would be a retrograde step unless further evidence is forthcoming to warrant such a procedure.

PRIME IMPORTANCE OF VASCULAR DISEASE

Despite the above arguments I do not wish to overemphasize the potential protective value of insulin in diabetes. Now that coma is a relatively minor problem, the importance of diabetes does not lie in its carbohydrate control but in its vasculopathies—retinopathy, neuropathy (assuming that this is basically vascular), nephropathy, and coronary and peripheral vascular disease. The blood sugar of itself is a matter of little importance. Although good control of diabetes as measured by glucose estimations may partially prevent the specific diabetic vasculopathies, yet it has little or no effect on the development of coronary heart disease.[9] We have observed this in figures from our own clinic. Normally, pre-menopausal women are considerably protected from the clinical manifestations of coronary atheroma by the very fact of their womanhood. In this respect diabetes abolishes the advantage of being born a woman. If, however, the coronary arteries can really be protected by a low intake of saturated fat, then surely the very first place in which this type of diet should be advised is the diabetic clinic? If the carbohydrate intake is increased and socalled 'control' rendered more difficult, is there any evidence at all that this would matter? It seems to me that many 'diabetic diets' being used today are probably atherogenic. As recently as June 1958 a report of the Council on Food and Nutrition (US) recommended that 40% of calories in a diabetic's diet should come from fat. Admittedly a small face-saving, and rather ingenuous, rider was added: 'with unhydrogenated vegetable oils substituted to a considerable extent for hard cooking fats'. Comment on the utter inadequacy of such advice should be unnecessary. There is certainly less evidence that the *specific* diabetic vascular lesions might be reduced by a lowered fat intake, but this is something that must be investigated.

CONCLUSION

I think that all this may be summarized by the suggestion that insulin, and even possibly the oral sulphonylureas, may have a greater potentially protective action in diabetes than we realize, but that drugs alone are not likely to solve the real clinical problem of diabetes—the vascular one. We still do not know how best to treat diabetes and are only just beginning to think about preventing it.

I should like to take this opportunity of thanking the British Insulin Manufacturers and especially Dr. F. Wolff for arranging the symposium; also Prof. J. F. Brock and Dr. J. H. Sheldon for reading this manuscript. Drs. N. Woolf and J. A. H. Campbell are responsible for the photomicrographs of the islets (Fig. 2).

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