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Yttrium 90 Needle Implantation in Diabetes: Correlation Between Degree of Hypopituitarism and Retinopathy Response

Patients with diabetic retinopathy have been studied by retinal photography and measurement of corrected visual acuity before and after pituitary implantation. By tests of pituitary function the patients were classified into three grades of hypopituitarism (Joplin *et al.* 1965). At one year post-implant approximately 100 eyes are available for assessment. The retinopathy components that were reversible by operation were hæmorrhages (and micro-aneurysms), new vessels in the retina and venous irregularity; for most of these components there was a rising frequency of improvements with increasing degrees of hypopituitarism. A similar trend was seen with visual acuity.

A detailed report is being published elsewhere (Oakley *et al.* 1967 in preparation).

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Relation of the Complications of Diabetes to the Clinical State

From the viewpoint of the clinician, the important question to be answered is to what extent the degenerative changes occurring in diabetes are attributable to hyperglycæmia, and hence whether these changes can be prevented by lowering the blood sugar levels. Our confidence in the simple thesis that diabetes is due to a lack of insulin has been seriously undermined in recent years. With the advent of more reliable techniques for measuring the amount of circulating insulin, it has been demonstrated that maturity onset diabetics show levels of circulating insulin greater than those found in normal controls, and even ketotic diabetics may show insulin-like activity to be present in the plasma when measured by epididymal fat techniques. There is evidence in some diabetics that insulin may be present in a form which prevents its normal action. Hence it is at least possible that diabetics inherit or acquire metabolic defects which could immobilize insulin on the one hand and independently cause changes in the microvascular system, the eyes, nerves and kidneys, on the other. If this were so, hyperglycæmia could occur without degenerative changes; and degenerative changes might occur even though the blood sugars were normal.

Several aspects of diabetes make the clinician doubt that lack of insulin and hyperglycæmia are responsible for all the complications that occur. One of the most baffling observations is the frequency with which women who develop diabetes have given birth to large babies in previous years, sometimes thirty or forty years previously. Stillborn babies of these mothers often show considerable hypertrophy of the islet cells of the pancreas. Clearly some metabolic or hormonal derangement must be responsible for these changes but they occur long before any detectable abnormality of glucose tolerance. Again, it is not uncommon for newly diagnosed diabetics to present with characteristic changes of neuropathy or retinopathy already present. Of course moderate symptomless hyperglycæmia may have existed for some time before the patient sought advice but it is also possible that these degenerative changes preceded elevation of the blood sugar. Ellenberg (1961) stresses that neuropathy can occur in patients with normal blood sugars and before the presence of diabetes becomes apparent. Liebow *et al.* (1955) have shown that newly diagnosed diabetics already have an increased tendency to coronary artery disease. If in fact these changes were due to lack of insulin, it would be reasonable to expect administration of insulin to prevent them but unhappily this does not occur. For example, the incidence of retinopathy in diabetics increases steadily as the years go by and appears uninfluenced by insulin therapy. Again, there seems to be no correlation between insulin requirements and the extent of the damage, a disparity epitomized by the following two cases:

Case 1
Male, developed diabetes when aged 19. He then weighed 16 st. 7 lb and weight reduction soon led to normal blood sugars. He attended the clinic only sporadically. He developed severe retinal and renal changes and died of uræmia only nine years after the onset. Post-mortem confirmed extensive diabetic glomerulosclerosis in both kidneys.

Case 2
Male, first diagnosed at the age of 5. He has not been under any supervision for most of the time and took 64 units of globin insulin daily. Yet, thirty-two years later, he has only minimal retinal changes and no clinical evidence of renal involvement.

When we come to assess the value of treatment in delaying degenerative changes, difficulties soon become apparent. Most of the earlier surveys relate the incidence of such changes to the control of the diabetes; but there is no meaningful or constant definition of the term 'control'. In fact the term 'control' often refers to a mixture of different factors such as the frequency of diabetic coma or hypoglycæmic attacks, the degree of glycosuria and acetonuria, the blood sugar levels and especially the care with which the patient follows the diet. In this last respect, some clinics insist that all forms of food should be regulated while others feel that only carbohydrate foods should be measured, usually in 10 g units. In our clinic we use a standard diet sheet in which all forms of food are measured, and variety is provided by lists of alternatives for each item of food.

To what extent is meticulous adherence to the dietary regime successful in reducing blood sugar levels? An assessment of the dietary habits of 111 insulin diabetics was made by two observers unacquainted with their diabetic records. Patients were divided into groups. Group 1 were those who weighed their food and adhered strictly and regularly to their dietary regime. Group 2 were patients who understood the principles of their diet and adhered to it in a general way. Group 3 either did not bother about the diet at all beyond avoiding sugar or found that circumstances made it impossible for them to follow a regular diet. Post-prandial venous blood sugars were taken at clinic visits in the afternoon, usually at intervals varying from one to three months, with a minimum of 15 readings for each patient, the average number of observations being 24. These patients had all been attending the clinic for some years. Each patient was assessed not only for the mean blood sugar levels but also for the mean of the standard deviation as an expression of the way in which the blood sugar readings fluctuated from visit to visit.

Table 1
Dietary groups

	Group 1	*Group 2*	*Group 3*
No. of cases	17	60	34
Mean age (years)	44	44	42·5
Duration of diabetes (years)	8·0	11·6	11·7
Mean insulin dose (units)	51	57	55
Mean blood sugar (mg/100 ml)	209	186	205
Mean of the standard deviations	78·6	81·0	88·7

Insulin-dependent diabetics (111 cases) grouped according to their dietary habits. Group 1 were meticulous, Group 3 observed no restrictions (*see* text)

Table 2
Hypoglycæmic attacks related to dietary groups

	Group 1	*Group 2*	*Group 3*
Total No. of cases	17	60	34
No. with 'mild' attacks	8	27	32
No. with 'severe' attacks	9	33	2

Insulin-dependent diabetics who were least careful of their diet suffered fewest severe hypoglycæmic attacks (*see* text)

As can be seen from Table 1, there appeared to be no significant correlation between the degree of dietary care and the height of the blood sugar levels, or between the degree of dietary care and the extent to which the blood sugars fluctuated. Indeed, those who took least trouble with their diet seemed least liable to severe hypoglycæmic attacks (Table 2), perhaps because they relied on their appetite rather than on dietary rote, but perhaps because only patients not liable to hypoglycæmic attacks could afford to ignore the rules. Clearly sporadic post-prandial blood sugars cannot be an accurate guide to levels during the rest of the day or between visits. Nevertheless when the same technique was applied to groups of non-diabetics (9), 'diet only' diabetics (20), and 'tablet' diabetics (25) for a minimum of six readings, it soon became apparent that the method had validity (Table 3). Normal patients not only have lower mean blood sugar levels but these blood sugar readings are much more constant for each patient. All diabetics have raised blood sugars whatever the treatment, and the blood sugar levels fluctuate more than in non-diabetics.

Table 3
Sporadic post-prandial blood sugars. Comparison between non-diabetics and various groups of diabetics

	Mean blood sugar (mg/100 ml)	*Mean of the standard deviations*
Normals	78	12·2
'Diet' diabetics	135	28·4
'Tablet' diabetics	147	33·0
Insulin-dependent diabetics	195	83·0

If meticulous care in following the diet is unsuccessful in controlling blood sugar levels in insulin-dependent diabetics, is there any evidence that it reduces the incidence of complications? In a recent prospective study of 108 juvenile diabetics, Knowles *et al.* (1965) allowed the children a normal unmeasured diet. Advice was given in general terms and patients were warned not to become overweight. After ten years' observation, it was found that although hyperglycæmia was common, the prevalence of degenerative complications was similar to that reported from other clinics which laid stress on a measured and restricted diet. The general progress of these young patients compared favourably with those reported to be following measured diets.

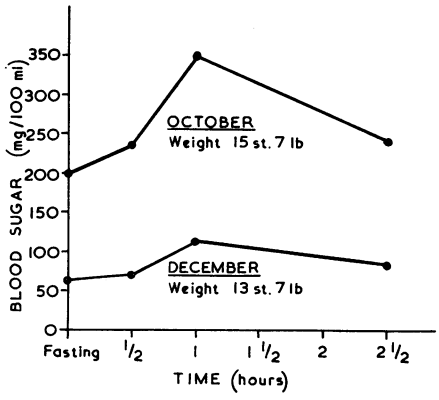

Fig 1 *Effect of dieting on glucose tolerance curve in an obese man aged 68*

This evidence is not to say that diet has no place in the management of diabetes. In overweight diabetics it has been abundantly demonstrated that reduction of weight leads to increased tolerance of glucose. For example, Fig 1 illustrates how a somewhat overweight man developed diabetes with an abnormal curve and how simple dietary restriction and loss of weight led to normal glucose tolerance. In insulin-dependent diabetics overeating leads to obesity with increasing insulin requirements while too low a carbohydrate intake disposes to ketosis. Nevertheless, it is clear that our present approach to diet in insulin-dependent diabetics needs rethinking. More attention must be paid to the fat and protein content of the diet. I will not discuss the merits of the various types of insulin in controlling blood sugar levels. In brief, in more severe diabetics, in young people, and during pregnancy, it is necessary to give insulin twice a day, usually soluble insulin, sometimes with the addition of a long-acting insulin.

Is hyperglycæmia responsible for the degenerative changes? Keen *et al.* (1965) recently conducted a large-scale survey at Bedford and were able to demonstrate a real association between the levels of glucose tolerance and various manifestations of arterial disease. This association held true even at those levels of blood sugar at which the diagnosis of diabetes was considered doubtful. They concluded that even symptomless impairment of glucose tolerance appeared an important accompaniment of atherosclerotic disease. In our own cases we compared a group of insulin-dependent diabetics having high blood sugars with a similar group having lower blood sugars. Each patient was assessed for evidence of vascular disease, retinopathy, neuropathy and renal disease by an observer unaware of the blood sugar findings. Three groups were defined, those with no complications, those with mild changes and those with severe complications. Although delineation between these groups cannot be exact, it seems (Table 4) that there is a higher incidence of severe complications in those with higher blood sugar levels (significance $P=0{\cdot}1$). Pirart (1965) reached a similar conclusion in his study of diabetic neuropathy. He used blood and urinary sugar levels as his main criteria of control, commenting that this excluded any subjective evaluation such as the degree of co-operation of the patient. In a large series of 1,041 cases he found a significantly higher percentage of neuropathy, retinopathy, arterial obliteration and nephropathy in those with higher blood sugar levels. On the other hand, Knowles *et al.* (1965) found no difference in the blood sugar levels in two groups of juvenile diabetics, one with retinopathy, the other without.

Table 4

Complications. Comparison of groups with high and low mean blood sugars in insulin-dependent diabetics

No. of cases	*Mean age (years)*	*Duration of diabetes (years)*	*Mean blood sugar (mg/100 ml)*	*Complications*		
				Nil	*Mild*	*Severe*
22	44·5	10·4	259	8	8	6
23	41·8	10·5	135	15	5	3

Finally, there are two other aspects of this subject which offer support to the thesis that diabetic degenerative changes are due directly to lack of insulin and not to associated hereditary defects: (1) In chronic pancreatitis and in hæmochromatosis, both of which can be assumed to lead to diabetes by mechanical destruction of the pancreas, retinopathy and glomerulosclerosis may develop. (2) Bloodworth (1965) has been

able to demonstrate the development of nodular glomerulosclerosis and retinopathy in dogs rendered diabetic by injections of growth hormone or by the destruction of islet cells with alloxan.

Faced with this conflicting evidence, my conclusion is that the degenerative complications of diabetes appear to be related in part to the degree of hyperglycæmia but probably other metabolic abnormalities play a more important role. In the present state of our knowledge it seems desirable to aim at keeping the blood sugar levels as near normal as possible, although it must be confessed, particularly in insulin-dependent diabetics, that our current approach is not very successful in this direction.

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