REVIEW

Pathogenesis of Genetic Diabetes Mellitus
Further Development of a Hypothesis

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The old concept of insulin deficiency as the basic mechanism in the development of diabetes in man has, in recent years, seen a revival. It has been amply demonstrated that not only the ketosis-prone juvenile but also the mild mature-onset diabetics and even latent diabetics (with decreased glucose tolerance only) respond to glucose with a subnormal elevation of plasma insulin (Yalow and Berson, 1960; Cerasi and Luft, 1967 a; Seltzer et al., 1967; Parker et al., 1968).

For this reason we presented some years ago the working hypothesis that a diminished insulin response to glucose is the basic pathogenic factor on which foundation the different stages of the diabetic syndrome develop (Cerasi and Luft, 1967 b). The presence of low insulin response in healthy monozygotic twins of diabetic patients indicates that this insulin deficiency is inherited and precedes the appearance of decreased glucose tolerance (Cerasi and Luft, 1967 c; Pyke et al., 1970). We therefore concluded that the combination of normal glucose tolerance and decreased insulin response to glucose characterizes the so called prediabetic state (Fig. 1). With this definition, the frequency of prediabetes in normal adults (Cerasi and Luft, 1967 a) and children (Cerasi and Luft, 1970 a) was found to be about 20 per cent. Since the frequency of manifest diabetes is much lower, it is obvious that not all prediabetics will eventually develop diabetes. The term is used in order to designate the group of subjects in which diabetes mellitus may develop. “Low insulin responder” might be a more appropriate term in this connection.

The term “low responder” or “low response” refers to the promptness and the degree of insulin secretion in relation to the height of the glycemic stimulus. In our studies, insulin response to glucose was evaluated with the aid of an analogue computer model, which measures the response as a function of the intensity of stimulation used (Cerasi, 1967).

Four major questions emanate from these basic observations:

A. What is the mechanism for the deficient insulin secretion in prediabetes and diabetes?

B. Which mechanisms contribute to the maintenance of a normal glucose tolerance in subjects with deficient insulin secretion, and which are the factors that precipitate clinical diabetes in low insulin responders?

C. Does the deficient insulin secretion bring about any metabolic derangements in low insulin responders?

These problems have been dealt with by our group during the last five years, and some of the results will be discussed in the following.

A. The Mechanism of the Deranged Insulin Secretion

The specific function of the beta-cell is to release insulin and, no doubt, glucose is the most important physiological stimulus regulating insulin release. But there is still no agreement as to the mechanisms involved in this process. A number of metabolites and
metabolic pathways within the beta-cell have been suggested to be the mediators of glucose induced insulin release (for reviews, see Mayhew et al., 1969; Grodsky, 1970).

However, during the last few years data have accumulated which may lead to a revision of this concept. Indeed, several aspects of the glucose induced insulin release are difficult to explain solely on the basis of glucose metabolism in the beta-cell. Among these the following may be mentioned: 1. As seen in Figure 2, the response of insulin in portal vein blood to a glucose infusion is an extremely rapid one, reminiscent of a cybernetic phenomenon. The highest insulin concentrations are reached even before the injection of glucose is terminated. If one considers the delays involved in the transport of glucose and insulin, the rapidity of the phenomenon becomes even more striking. 2. An infusion of the beta-adrenergic blocker, propranolol, in doses that do not modify the basal levels of glucose and insulin in blood, reduces significantly the insulin response to glucose administration (Cerasi et al., 1969; Cerasi et al., 1972 a). This inhibition may
be reversed by the simultaneous administration of aminophylline which is supposed to diminish the breakdown of cyclic AMP within the cells. 

3. In subjects with naturally occurring low insulin response to glucose, aminophylline, in amounts insufficient to modify the fasting glucose and insulin concentrations, can correct the responsiveness of the beta-cell to a glucose load (Cerasi and Luft, 1969 a).

4. Small doses of epinephrine, down to 3 ng per kg body weight per minute, reduce very significantly insulin response to glucose (Cerasi et al., 1971).

5. The most direct evidence in this context are the results of Matchinsky et al. (1971) demonstrating that none of the glucose intermediary metabolites in the beta-cell is increased during glucose stimulated early insulin release.

On the basis of findings as those related above, we have suggested that glucose acts on the beta-cell along two, in principle independent lines (Cerasi and Luft, 1970 b). Firstly, glucose is utilized as a substrate and, i.a., provides energy as in other living cells. Secondly, glucose acts on the beta-cell in the way a hormone acts on its target cell, generating a signal which transmits information from the extracellular space to the specific function of the cell (Fig. 3). In other words, glucose may stimulate directly a specific (cell membrane?) receptor in the beta-cell, giving rise to a signal which is transmitted to the cellular mechanisms controlling the discharge of insulin. This view of a dual role of glucose in insulin secretion implies that the insulinogenic action of glucose, at least partially, is dissociated from glucose metabolism in the beta-cell.

The demonstration by Kanazawa et al. (1971) that pyruvate and tolbutamide induced insulin release is stimulated by inhibitors of glycolysis, such as 2-deoxyglucose and mannoheptulose, further support this concept. These glucose analogues may possess the capacity to stimulate the specific glucose receptors of the beta-cell.

How the insulinogenic signal of glucose is relayed from the glucose receptor to the actual site of insulin release in the beta-cell is not known. On the basis of data in the literature assigning a major role in insulin secretion to the cyclic AMP system (Sussman et al., 1966; Turtle et al., 1967; Malaisse et al., 1967; Lambert et al., 1967), and our own finding in humans with aminophylline and propranolol under various experimental and pathological conditions (Cerasi et al., 1969; Cerasi et al., 1972 a; Cerasi and Luft, 1969 a), we postulated that the signal generated by glucose might be mediated by an increase in the production of cyclic AMP in the beta-cell. This nucleotide would then activate the release of insulin,
probably through mechanisms involving translocation of calcium ions in the cell (Malaisse-Lagae and Malaisse, 1971).

Several authors have been unable to demonstrate changes in adenyl cyclase activity on glucose stimulation of the islets and, therefore, questioned the role of cyclic AMP on insulin secretion (Kipnis 1970, Montague and Cook 1971, Levey et al. 1972). However, recent findings in our laboratory and elsewhere (Charles et al. 1973) suggest that glucose may indeed act as an activator of adenyl cyclase in the pancreatic islets.

Although glucose may be the main insulin releasing agent in man, it is certainly not the only one. Amino acids, and of these especially arginine, are established insulinogogues. However, as demonstrated in a recent series of studies, arginine induces insulin release by potentiating the action of glucose on the beta-cells (Efendic et al., 1971, 1972). While arginine did not induce insulin release during hypoglycemia, the effect of glucose on insulin response was enhanced percentually to the same extent at all hyperglycemic levels tested. Thus, arginine seems to be a multiplicative potentiator of the glucose effect on the beta-cell (Efendic et al., to be published). Furthermore, the amino acid probably exerts its effect directly on the insulinogenic signal of glucose rather than through modification of glucose metabolism in the beta-cell (Efendic et al., 1971).

Similar results were obtained with another insulinogogue, the sulfonylurea tolbutamide, which also seems to induce insulin release by modulating the insulinogenic signal of glucose (Widström and Cerasi, 1973 a, b, c). However, while arginine acts as a multiplicative potentiator of the glucose signal, tolbutamide sensitizes the beta-cell to glucose action: it causes a shift to the left of the glucose-insulin dose relationship without modifying the maximal effect of glucose.

The mechanism by which arginine and tolbutamide modify the insulinogenic signal of glucose is not yet clear. Probably both act at the cell membrane level (Fajans et al., 1971; Hellman et al., 1971; Lambert et al., 1971). Some indirect evidences suggest that the arginine action may result in increased formation of cyclic AMP (Efendic et al., 1972), whereas tolbutamide influences mechanisms distal to the formation of the nucleotide (Widström and Cerasi, 1973 c). The relationship between these secretagogues and the glucose signal is illustrated in Figure 3.

Against the background of the model presented in Figure 3, a deficiency in insulin secretion of the type seen in prediabetes and mild diabetes may be explained by one of the following alternatives: a reduction of the number of beta-cells or their insulin content; vascular changes (microangiopathy of the islets) which impair the passage of insulin to the blood stream and of glucose into the islets; impairment of glucose utilization of the beta-cells; impaired transmission in the beta-cell of the glucose-induced insulinogenic signal. The first three alternatives mentioned are unlikely explanations since, as we and others have demonstrated, a rather normal insulin release can be obtained both in prediabetics and mild diabetics by intravenous administration of tolbutamide (Varsano-Aharon et al., 1970) or glucagon (Simpson et al., 1968) or by glucose after pretreatment with theophylline (Cerasi and Luft, 1969 a).

Since the defect in insulin response is rather selective for glucose, we have postulated that an impairment in the transmission of the glucose signal might be the principal aberation in the beta-cell in prediabetes and diabetes (Cerasi and Luft, 1970 b). Agents like theophylline, which diminish the intracellular breakdown of cyclic AMP, enhance the signal evoked by glucose, and thus tend to normalize insulin response.

We have recently obtained more evidence indicating that the poor insulin response in the prediabetic and mild diabetic indeed is caused by a diminished sensitivity of the beta-cell for glucose (Cerasi et al., 1972 b). In normal subjects, insulin response increases
with the degree of the hyperglycemic stimulus up to a blood glucose concentration of 400–500 mg per 100 ml, the response then levelling off (Fig. 4). This insulin profile applies both to the early and late responses. In the prediabetic subjects, insulin response is only slightly stimulated up to a blood glucose level of 300–400 mg per 100 ml, in contrast to the steep rise in the normals. However, further elevation of the blood sugar to the range of 450–700 mg per 100 ml is accompanied by a substantial insulin response, some prediabetics now presenting a completely normal pattern of insulin release. In terms of dose-response relationship, this means a parallel shift of the prediabetic curve to the right of the normal one. A comparison of the dose-response curves for the early and late responses in the prediabetics demonstrates a similar behaviour of both phases, although the magnitude of the late response is larger. Thus, the defect in insulin secretion is not limited to the early response. These findings imply that the prediabetic beta-cell is equipped with all the necessary requisites for insulin response to glucose but that the ability of the beta-cell to recognize the hyperglycemic information is diminished. To our mind, the most plausible explanation is that the sensitivity of the glucose receptor is decreased in the prediabetic beta-cell.

As shown in Figure 4, the situation in the mild diabetic in this respect is similar to that in the prediabetic but the decrease in glucose sensitivity is more advanced. This is indicated by the further shift of the dose-response curves to the right. The situation in the ketosis-prone juvenile diabetics has not been studied in this respect. The defect in their beta-cells may be of a different nature.

The physiological implications of the above studies, where blood glucose concentration had to be elevated to values ranging from 500 to 1000 mg per 100 ml, are questionable. It then has to be remembered that, if a physiological stimulus of the beta-cell like food intake or even an oral glucose load is used, the range of blood glucose elevation needed for the secretion of insulin is much lower (for a review, see...

Fig. 5. The glucose-insulin dose-relationship during oral glucose tolerance tests. Triangles represent the control group, open circles the prediabetics and filled circles the mild diabetics. (Cerasi et al., 1973 a).

Marks and Samols, 1970). Indeed, in a recent series of experiments where various doses of glucose were given orally to normal controls, prediabetics and mild diabetics, it could be demonstrated that the glucose-insulin dose-response curves of the prediabetics and diabetics were again shifted to the right of those of the controls. Thus, while still demonstrating decreased sensitivity of the beta-cell to glucose, major insulin response could be obtained in the prediabetics and diabetics with blood glucose levels in the range of 180–300 mg per 100 ml (Fig. 5) (Cerasi et al., 1973 a).

B. The Regulation of Glucose Homeostasis in Prediabetes and Factors Involved in the Transition from Prediabetes to Diabetes

The simplest explanation for the development of glucose intolerance in a prediabetic subject would be further gradual deterioration of the insulin response to glucose. This has been suggested by Seltzer et al. (1967). In our earlier papers, we emphasized that the insulin deficiency in many instances of prediabetes is of the same degree as in the manifest stage of the disease (Cerasi and Luft, 1967 a). In addition, decreased insulin response of the same magnitude is also found in children, suggesting that the pattern of insulin release is not much modified with time (Cerasi and Luft, 1970 a). However, these studies were performed using one single standard load of glucose which induced a hyperglycemia of 300–400 mg per 100 ml. As can be seen from Figure 4, this load discriminated effectively the prediabetics from the normal insulin responders. However, it did not differentiate prediabetics from mild diabetics, although this latter group obviously showed a further decrease in glucose sensitivity. Therefore, it cannot be excluded that, in some prediabetic subjects, the sensitivity of the beta-cell to glucose may further diminish with time, and be a significant factor for the development of glucose intolerance.

However, the above reasoning is not sufficient to explain the normal glucose tolerance in the low insulin responders that demonstrate so clearly a difference in insulin output compared to the control subjects. We postulated earlier, therefore, the presence of some mechanisms that might be operating in the prediabetics in order to compensate for the insulin deficiency (Cerasi and Luft, 1967 b). Our demonstration, in the prediabetic subjects, of decreased insulin response also to orally administered glucose (Cerasi et al., 1973) excludes the possibility of the presence of intestinal factors which might stimulate the beta-cells and thereby correct the glucose insensitivity as demonstrated on i.v. glucose.

We have earlier demonstrated that prediabetics are more sensitive to exogenous insulin (Cerasi and Luft, 1969 b). The site of this increased insulin sensitivity, on the basis of studies on the conversion of $^{14}$C-pyruvate to $^{14}$C-glucose and $^{14}$CO$_2$, was earlier sug-
Inhibition of Hepatic Glucose Output during Glucose Infusion

Fig. 6. Inhibition of hepatic glucose output during glucose infusion in low insulin responders (filled circles) and controls (open circles). Vertical bars denote S.E.M. (Wahren et al., 1973).

These findings suggest that the prediabetic subject may keep the glucose tolerance normal by shutting off the production of glucose at an earlier stage of glucose intake. The mechanisms responsible for this adaptation are not clear to us. Anyway, failure of such a mechanism might be responsible for the appearance of glucose intolerance. We have no data available at present which would permit us to conclude that there is a transition from supranormal regulation of hepatic output of glucose over a normal one to the hepatic hyporesponsiveness demonstrated in diabetes (Fig. 7).

In addition to the above mechanisms, glucose intolerance may be induced by factors that diminish insulin sensitivity and thus increase the demand of the organism for insulin. A prediabetic subject, because of his
limited capacity to increase insulin output, would be more vulnerable to this new situation. Obesity and acromegaly are two such conditions. We and others have previously demonstrated that those obese and acromegalic subjects who demonstrate low insulin response also show decreased glucose tolerance or overt diabetes (Luft et al., 1968; Karam et al., 1965; Luft et al., 1967). Obesity is an obvious factor in the development of diabetes. As to HGH, it is not known whether the well-known diurnal fluctuations in its secretion (Roth et al., 1963; Hunder et al., 1965) play a role in the precipitation of diabetes.

The insulin resistance of obesity and acromegaly has hitherto been discussed mainly in terms of the response of the stimulus.

C. Metabolic Consequences of Low Insulin Response in Non-Diabetic Subjects
The important question is whether a low insulin response does indeed represent a pre-
diabetic state, i.e., a disturbed hormonal situation, or simply reflects the left tail of a Gaussian distribution of normal pancreatic function. If, as we have postulated, the first alternative is the correct one the majority of subjects with genetic diabetes should originate from the population of low insulin responders. One must remember, however, that in that case not more than 10 per cent of the pre-diabetics can eventually develop overt diabetes (assuming an incidence of manifest diabetes of 2 per cent) and about 30 per cent will have decreased glucose tolerance (incidence 6 per cent) sometimes during their adult life. Thus, substantial groups of controls and low insulin responders have to be followed for decades before a definite answer to the above question can be obtained.

So far, of 23 prediabetics and 90 controls, which have been followed for 3–8 years with repeated i.v. glucose tolerance tests, two of the subjects with low insulin response now have permanently decreased glucose tolerance, one of them with slight fasting hyperglycemia at one occasion. In the control group one subject has developed decreased glucose tolerance.

Do the prediabetic subjects carry any metabolic stigmata akin to the diabetic individuals? We have tried to explore this question by studying, in the prediabetic subjects, certain parameters that are well known to be deranged in diabetes.

By definition and by selection low insulin responders have a normal glucose tolerance. However, the high insulin responders demonstrate a significantly higher k-value in the intravenous glucose tolerance test than the low responders (1.90 ± 0.69 versus 1.56 ± 0.40, p < 0.01) indicating a tighter control of the glucose tolerance. Furthermore, the rate of peripheral utilization of glucose, calculated from studies with liver vein catheterization (see below), was significantly lower than normal in low insulin responders (Cerasi et al., 1973) and monozygotic healthy twins of diabetic subjects (Wahren et al., 1973). These facts probably make the low insulin responder more vulnerable to factors which tend to lower the glucose tolerance. In such subjects the diabetic range would thus be reached more easily.

A similar trend towards a diabetic type of metabolism—in this case lipid metabolism—was demonstrated in some low insulin responders during muscular exercise (Nordlander et al., 1973). Lipolysis is accelerated to a greater degree in diabetic subjects than in controls during a submaximal work load, resulting in a more marked elevation of the plasma levels of glycerol and FFA (Fig. 8). Low insulin responders usually behaved normally in this respect. However, in four out of ten such individuals glycerol and FFA in the plasma reached diabetic levels (Fig. 9). Thus, these subjects could be considered as normals in respect to glucose tolerance but as diabetics at the adipose tissue level. Again, a group of prediabetics demonstrated stigmata of the diabetic state.

Another set of findings pointing to a deranged metabolism in prediabetes was obtained through studies of the newborn infants of prediabetic mothers. It is well known that diabetic mothers often give birth to children with higher than normal glucose tolerance and a tendency to develop hypoglycemia. We have investigated a group of low insulin responders throughout pregnancy (Edström et al., to be published). None of these women developed latent or manifest diabetes. On the other hand, preliminary data show that, during the first 24 hr of life many children of prediabetic mothers behave like those of diabetic subjects regarding tolerance. Thus, while 8 out of 14 newborns of healthy mothers had k-values below 1.0 and only 2 demonstrated a value above 1.30, in the children of prediabetic women only 2 out of 11 had a k-value less than 1.0, while in 5 a value above 1.30 was found. In other words, a substantial percentage of newborns of low insulin responders may behave like children of diabetic mothers in spite of the fact that none of their mothers developed decreased glucose tolerance during
Fig. 8. Changes in the concentration of plasma glycerol during exercise in normal subjects and insulin dependent diabetics. The shaded area denotes the +3 S.D. of the mean elevation in the normal group. The curves illustrate the individual responses in the diabetic subjects. (Nordlander et al., 1972).
pregnancy. The factor(s) responsible for the early maturation of the islet apparatus in the offspring of prediabetic women is completely obscure.

It can be seen from the above data that low insulin responders, in addition to deranged insulin response to glucose, may share other characteristic abnormalities with diabetic subjects. Our findings give rise to a number of questions that remain to be answered: are there any basic differences between low insulin responders with and without the above metabolic abnormalities? In other words, of the total group of low insulin responders, are the real prediabetics only those who demonstrate such metabolic derangements? Or do these derangements come as late consequences of an inherited insulin deficiency? Can the metabolic abnormalities we have demonstrated so far occur successively in one and the same subject? If so, does the abnormal metabolic state of the diabetic result from the successive addition of “partial abnormalities” already present during the prediabetic stage? Finally, what are the long-term consequences of these “partial abnormalities” in subjects who remain prediabetics throughout life? In relation to this latter question, the well established connection between the diabetic state and arteriosclerotic disease has to be emphasized. It has been amply shown that latent diabetes occurs in a high frequency in patients with ischemic heart disease. Furthermore, it was recently claimed that patients with vascular
disease mainly localized to the small vessels had an impaired insulin release to glucose (Ghilchik and Morris, 1971). It seems imperative, therefore, to investigate the relationship between vascular disease and prediabetes. This subject has recently been discussed by us in detail (Efendic et al., to be published).

D. Future Aspects of the Prevention and Treatment of Diabetes

Against the background of our actual information as presented above, two principal approaches to the prevention and treatment of genetic diabetes mellitus may be visualized. Firstly, the common ground for all stages of diabetes—the inherited decrease in insulin response—may be normalized. Secondly, the diabetic individual may be brought back to the prediabetic stage by measures inducing supranormal regulation of glucose output by the liver.

An attempt to normalize insulin output in diabetes forms the basis for the use of oral hypoglycemic agents. The goal of this type of treatment should be to induce a shift of the diabetic and prediabetic glucose-insulin dose-response curves towards the range of the normal one (for a detailed discussion of this topic, see Widstrom and Cerasi, 1973 a, b, c). It should be possible to develop specific agents which either increase the sensitivity of the beta-cell receptor for glucose, or which amplify the insulinogenic signal generated by glucose by acting at a later link of the signal chain. Our finding that aminophylline may correct insulin response to glucose in pre-diabetic subjects exemplifies this.

As discussed previously, we are at present ignorant of the factors that keep the regulation of hepatic glucose output at a supranormal level in the prediabetic, and that are at fault in the diabetic subject. Clarification of these mechanisms may lead to the development of agents capable of shifting hepatic glucose production towards the prediabetic direction.

We have already emphasized earlier in this presentation that the prediabetic state is not devoid of metabolic consequences (including lipid metabolism). We are of the opinion that a long-term study of the effects of low insulin response on, i.a., the cardiovascular system would be most appropriate. Should a correlation between low insulin response and arteriosclerosis become evident, the early correction of the deficient insulin response would become a matter of paramount importance and exceed the scope of diabetes mellitus as such.

Conclusion

The prediabetic state is characterized by normal glucose tolerance and decreased insulin secretion on glucose stimulation. In spite of earlier belief, this state is not always devoid of metabolic consequences. Thus, the disappearance rate of intravenously administered glucose (k-value), although within the normal range, is significantly lower than in the control group. In some prediabetics, the lipolytic response to physical exercise is increased to the extent found in manifest diabetes. Furthermore, prediabetic mothers may give birth to children with diabetic foetopathy. Many of the newborns of these women show high k-value as do children of diabetic women.

The decreased insulin output of prediabetics and mild diabetics is probably due to a decreased sensitivity to glucose of a specific receptor of the beta-cells of the pancreas. This suggestion is supported by the finding that both prediabetics and mild diabetics can release normal amounts of insulin provided blood glucose is raised to 500–1000 mg%.

The transition from prediabetes to diabetes may be induced by several factors such as progressive deterioration of insulin output, or addition of diabetogenic factors like obesity and HGH-overproduction. Hepatic glucose output in the prediabetic is regulated with a higher than normal efficiency, thus compensating for the deficient insulin secretion. The failure of this important mechanism may be a
major precipitating factor for diabetes.

In the light of the foregoing findings it may be predicted that the future prevention and treatment of diabetes mellitus will depend on the development of agents that: a) correct the sensitivity of the glucose receptor of the beta-cells, and b) stimulate the ability of the liver to suppress its glucose output.

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