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Diabetes Mellitus: A "Thrifty" Genotype  
Rendered Detrimental by "Progress"?

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FOR THE POPULATION GENETICIST, diabetes mellitus has long presented an enigma. Here is a relatively frequent disease, often interfering with reproduction by virtue of an onset during the reproductive or even pre-reproductive years, with a well-defined genetic basis, perhaps as simple in many families as a single recessive or incompletely recessive gene (cf. Allan, 1933; Pincus and White, 1933, 1934; Harris, 1950; Steinberg and Wilder, 1952; Lamy, Frézal and de Grouchy, 1957; Steinberg, 1959; Post, 1962a). If the considerable frequency of the disease is of relatively long duration in the history of our species, how can this be accounted for in the face of the obvious and strong genetic selection against the condition? If, on the other hand, this frequency is a relatively recent phenomenon, what changes in the environment are responsible for the increase? Current developments in the study of this disease suggest an explanation with important biological ramifications.

"THRIFTINESS" OF DIABETIC GENOTYPE PRIOR TO ONSET OF  
DIABETES MELLITUS

There is now much evidence to indicate that the individual predisposed to diabetes differs metabolically from the non-predisposed from birth onward. The frequency of over-sized infants among the offspring of women with overt or subclinical diabetes is well known (e.g., Bowcock and Greene, 1928; Bix, 1933; Allen, 1939; Miller, 1945, 1956; Kriss and Futcher, 1948; Gonce, 1949; Gilbert, 1949; Brosset and Werkö, 1950; Moss and Mulholland, 1951; Jackson, 1952; Pirart, 1955; Hsia and Gellis, 1957, etc.). This phenomenon, which may antedate the development of clinical diabetes by 30 years, has customarily been regarded as an expression of the mother's diabetes. The difficulties in duplicating this phenomenon in experimental animals rendered diabetic by alloxan (Miller, 1947, but see Lazarow, Kim and Wells, 1960) leaves some room for doubt as to whether this concept offers a complete explanation. Maternal genotype and phenotype may be only one factor in the etiology of the phenomenon. Inasmuch as from the genetic standpoint these children constitute a high risk group, and in view of the report that the juvenile diabetic at birth averages some 100 grams heavier than his non-diabetic siblings (Nilsson, 1962, but see White, 1960), the possibility must be considered that this phenomenon is also in part an expression of the infant's predisposition. Some evidence to this effect may be drawn from the observations of Sheldon (1949)

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on rapidly developing maternal obesity, in that women who presented with this problem, of whom a significant proportion had overt or subclinical diabetes and to whom large infants were often born, themselves often had been large infants.

What is lacking is evidence concerning the relative risk of the development of diabetes in the normal-birthweight siblings of these individuals. Somewhat more cogent evidence regarding the role of infant genotype in birthweight comes from the reports that the infants born to normal mothers with diabetic husbands also have an increased birthweight (Jackson, 1952; Siegeler and Siegeler, 1960; Pyke, 1961; Nilsson, 1962). Children who develop diabetes tend to be somatically advanced for their age (White, 1939; Wagner, White and Bogan, 1942; Nilsson, 1962). The menarche has occurred, on the average, about a half to three-quarters of a year earlier in the diabetic woman who developed her disease after the age of 20 than in her siblings who did not later develop diabetes (Arduino and Ferreira, 1958; Post and White, 1958; Post, 1962). Theoretically (cf. Post and White, 1958) this might lead to earlier onset of childbearing and even to an increase in average fertility on the part of those with late-onset diabetes, capable of offsetting, at least in part, the impaired reproductive performance of those with early onset diabetes. The actual data on this point are consistent with a fertility differential in favor of the diabetic, but, as pointed out by Post and White (1958), are inadequate in several respects. Finally, it has been suggested that the overweight individual of 40 or 50 with mild diabetes is not so much diabetic because he is obese, as he is obese because he is of a particular (diabetic) genotype (Vallance-Owen and Lilley, 1961b).

The foregoing considerations may be taken to indicate that in the early years of life the diabetic genotype is, to employ a somewhat colloquial but expressive term, a "thrifty" genotype, in the sense of being exceptionally efficient in the intake and/or utilization of food. A frequently mentioned alternative viewpoint, that diabetes, especially the childhood type, develops in predisposed individuals who have (unrelated) disturbances in pituitary and other endocrine functions, requires the postulate of a second order interaction which seems unnecessary in view of the evidence that a very high proportion of those genetically predisposed ultimately develop diabetes (Post, 1962a). The precise physiologic basis for this "thriftiness" remains unclear. There are obvious possibilities. Thus, if after stimulation of the islets of Langerhans they continued to function longer in the predisposed than in the normal, this could depress the blood sugar level unduly, resulting in hunger and an increased food intake. In this connection, Seltzer, Fajans and Conn (1956) have emphasized the frequency of mild spontaneous hypoglycemia in early diabetics following a glucose tolerance test. They interpreted this as due to a lag in insulin production in response to the stimulus of a rising blood sugar level, resulting in a supernormal stimulus to the islets of Langerhans, followed by discharge of an amount of insulin sufficient to produce transient hypoglycemia. In the light of developments to be mentioned shortly, one can question whether this lag in insulin production, for which there is not only indirect but (see below) direct evidence, is real or only ap-

parent; the important fact at this point is the occurrence of hypoglycemia in some early diabetics following glucose loading.

A second possible mechanism to be considered involves a pancreas more rapidly responsive to increases in the level of blood glucose. In this connection it must be remembered that during the first 99 per cent or more of man's life on earth, while he existed as a hunter and gatherer, it was often feast or famine. Periods of gorging alternated with periods of greatly reduced food intake. The individual whose pancreatic responses minimized post-prandial glycosuria might have, during a period of starvation, an extra pound of adipose reserve. In this connection Baird and Farquhar (1962) have recently demonstrated a striking increase in the ability of newborn infants of diabetic mothers to handle a glucose load, this accompanied by a marked elevation in plasma insulin-like activity as evaluated by the rat diaphragm technique. Six infants were tested; all exceeded the greatest response observed among the six controls. Genetic expectation is for approximately half of the children of diabetic mothers to develop diabetes. The fact that all six children exhibited the exaggerated response would seem to indicate that, like heavy birthweight, this is at least in part a manifestation of mother's genotype (*i.e.*, a response to elevated maternal blood glucose levels). On the other hand, there was considerable variability in the degree of the response, and the possibility must be considered that the infant's genotype is playing a role. Extension of the series and long range follow-up studies would shed light on this question.

#### THE PHYSIOLOGIC BASIS FOR DIABETES MELLITUS

These thoughts suggest that the diabetic genotype is at the outset distinguished by a greater-than-normal availability of effective circulating insulin at some stage in the cycle of responses that follow food intake. How to reconcile this with the relative insufficiency of later years? In the past there have been vague references to "organ exhaustion." This suggestion, from its inception unlikely as a general explanation in view of the great functional reserve of all endocrine and exocrine glands, has now been rendered untenable as the primary cause by a series of developments. Some 10 years ago it was demonstrated that many mild diabetics when in the fasting stage have approximately normal amounts of plasma insulin-like activity (Bornstein and Lawrence, 1951). Subsequently, with the use of more sensitive techniques (rat diaphragm technique, immuno-assay), it has been shown that these mild diabetics when in the fasting state may actually often have somewhat elevated levels of serum insulin-like activity (Vallance-Owen, Hurlock and Please, 1955; Baird and Bornstein, 1957; Wright, 1957; Seltzer and Smith, 1959), and although there is a lag in the response to glucose loading, may ultimately show a much greater response than normal in terms of serum insulin-like activity (Yalow and Berson, 1960, 1961). The demonstration of normal fasting levels of serum insulin-like activity has been extended to severe, young, ketotic diabetic patients by the rat epididymal fat technique (Steinke, Taylor, and Renold, 1961). Furthermore, in a group of individuals with a very high expectation on genetic grounds of developing clinical diabetes (prediabetics), the mean level of serum

insulin-like activity in fasting blood samples as measured with the rat epididymal fat techniques was significantly elevated above control levels (Steinke, Camerini, Marble and Renold, 1961). All these prediabetics had normal oral glucose tolerance tests. Their mean age was not given.

The discrepancy which is detected in these various studies, between normal or increased assayable plasma insulin-like activity and evidence of an actual or potential relative insulin deficiency, has now been rendered intelligible by the recent demonstration of a substance or substances antagonistic to the action of insulin (anti-insulins) associated with the albumin fraction of the serum proteins of normal individuals (Vallance-Owen, Dennes and Campbell, 1958; Lowy, Blanshard and Phear, 1961; Vallance-Owen and Lilley, 1961a) and present in increased amounts in both the diabetic (Vallance-Owen, Hurlock and Please, 1955; Vallance-Owen, Dennes and Campbell, 1958; Vallance-Owen and Lilley, 1961b) and prediabetic (Vallance-Owen and Lilley, 1961b). One of these substances may be identical with the recently reported basic protein in normal blood serum capable of binding insulin (Antoniades, 1958; Antoniades *et al.*, 1958, 1960; Gundersen and Antoniades, 1960).

The normal metabolism of glucose must involve a balance between the action of insulin and these anti-insulins. In keeping with the usual mechanisms operative in physiologic balances, we may theorize that in the individual predisposed to diabetes, the postulated increased ability in the early years of life to release insulin provokes in time a relative overproduction of its antagonist. There is initially in those genetically predisposed to diabetes a balance between increased insulin production and an increased production of antagonist. Not until this balance is overcome by excessive antagonist production does clinical diabetes develop. In some individuals the imbalance comes early, but in others it may be delayed until quite late in life or even not develop at all, leading to the failures in the penetrance of the diabetic genotype for which there is genetic evidence. In the face of a long-standing, marked excess of antagonist, secondary changes may result in the islets of Langerhans, namely the hyalinization which has been so instrumental in leading to the older concept of "organ exhaustion," and as a result of these secondary changes the relative insulin insufficiency may increase. The ease of stimulation of antagonist production may vary from individual to individual, this factor also playing a role in the incomplete penetrance (in terms of diabetes) of the diabetic genotype. In this framework, and especially in view of the findings of Yalow and Berson (1960, 1961), we could reinterpret the important observations of Seltzer, Fajans and Conn (1956), referred to above, concerning spontaneous hypoglycemia in some early diabetics, as evidence for a (delayed) ability of the pancreas of some diabetics to compensate and over-compensate for the increased amounts of antagonist. Some evidence concerning the correctness of this reinterpretation might be expected from a study of the effect of anti-insulins on insulin values as determined by the immuno-assay technique of Yalow and Berson (1960), coupled with studies of the level of anti-insulin activity at fixed intervals during a glucose tolerance test.

At this stage in the development of the problem, several alternative concepts

of diabetes cannot be excluded with confidence. Thus, the hypothesis is still tenable of an initial hypoinsulinism, followed by a compensatory increase in beta cell function occurring perhaps through a feedback system controlled by the level of "active" insulin and stimulated by a pituitary insulotropic hormone, and this in turn followed by excessive production of the anti-insulin (Conn and Fajans, 1961). Likewise, it remains possible that the relative excess of antagonist comes first, with the high serum insulin levels the result of an attempt to compensate for this antagonist (Vallance-Owen and Lilley, 1961b). However, neither of these approaches would seem to account satisfactorily for the "thrifty" aspects and frequency of the diabetic genotype nor, in the case of the "antagonist" hypothesis, for the well-founded clinical observation that carbohydrate tolerance can often be re-established, even if only temporarily, in the mild, obese diabetic by proper diet and weight loss.

#### REASONS FOR THE HIGH FREQUENCY OF DIABETES MELLITUS TODAY

We come now to the problem posed by the relatively high frequency of the disease diabetes. Even if this is a situation of long standing, it seems unlikely that in the past it would have interfered with reproduction to the extent it does today (in the absence of appropriate medical care) because of the earlier age at which reproduction has tended to occur in the past. However, three lines of thought suggest that there has been a true increase in the frequency of the disease as more and more people have come to enjoy the blessings of civilization (see also Aschner and Post, 1957). Firstly, obesity appears to be, on the whole, a rarer phenomenon in primitive cultures than in our own. There is less opportunity to indulge a hypertrophied appetite, and/or the lower mean caloric intake and greater physical activity of these primitive groups provide less of a stimulus to insulin production; this in turn means less stimulation of the antagonist-producing mechanism. Secondly, the action of the adrenal steroids in bringing to light the subclinical diabetic (Fajans and Conn, 1954, 1961a), in addition to the well recognized effect of these compounds on gluconeogenesis (cf. Fajans, 1961), may also be through stimulation of antagonist production. Since the response of the adrenal cortex to alarm situations is now less often followed by motor activity than in the past, one may postulate a disturbance in the physiologic balance established in the course of human evolution. Thirdly, the well known glucose-mobilizing effects of adrenalin release are now not followed to the same extent by physical activity as seems to have been the case for primitive societies; since this calls for a greater insulin production than would otherwise be the case, here again is an opportunity for increased stimulation of the insulin antagonist mechanism. These latter two thoughts would tend to place diabetes in the poorly defined area of the "stress diseases" — and indeed, the physiologic evidence to this effect is right now at least as convincing as it is for regarding peptic ulcer and coronary hypertension as stress diseases.

The foregoing suggestions are not advanced as a universal explanation for all cases of diabetes mellitus not due to actual islet destruction. The existence of genetically determined abiotrophies and biochemical blocks is so firmly established that it would be strange indeed if there were not also a genetic mech-

anism responsible for a primary failure of the islets of Langerhans. However, the very high frequency of diabetes among the offspring of conjugal diabetics (Post, 1962a) as well as the fact that approximately 50 per cent of the middle-aged siblings of a diabetic patient manifest either overt diabetes, latent diabetes or a diabetic-type response to cortisone (Fajans and Conn, 1961b) certainly suggest that one genetic mechanism dominates the scene. The facts just reviewed would seem to favor a relative insulin overproduction at some stage in the food ingestion cycle as being the first phase in most diabetics — this would not be expected to be the case in a genetically determined biochemical block or abiotrophy.

#### HOW TO TEST THE HYPOTHESIS

The hypothesis which has been advanced regards genetically-determined diabetes mellitus as, for the most part, the result of an excessive production of insulin antagonists or anti-insulins. This excessive production is a secondary phenomenon due to over-stimulation of the antagonist mechanism by a greater-than-normal availability of insulin at some stage in the food ingestion cycle. In genetically determined diabetes mellitus the defect is postulated to be this relative "over-production" of insulin. It is argued that what we now must regard as an "over-production" with unfortunate consequences was, at an earlier stage in man's evolution, an asset in that it was an important energy conserving mechanism when food intake was irregular and obesity rare.

This hypothesis has the merit of being eminently subject to test. The key is a comparison of certain aspects of the metabolism of those predisposed to diabetes with those not so predisposed. This can be achieved by a long-range comparison, beginning at an early age, of the individual children of diabetic x normal marriages, some of whom will develop the disease and some not, or a comparison of children of marriages of two diabetics with the children of normal x normal marriages where neither parent has a family history of diabetes. The importance has already been mentioned of continuing observations of the responses to glucose loads of a series of children studied as infants by the techniques of Baird and Farquhar (1962) to determine whether the children with the most exaggerated responses to glucose are usually the ones to develop diabetes later. In addition the hypothesis suggests that some of the children of diabetics during their early years should not on the average attain as high blood sugar levels following a test meal and/or spill as much sugar in the urine as children whose family history was free of diabetes. Serum insulin assays might be expected to yield higher post-prandial levels in some of these children (in the absence of an elevation in antagonist level) either at the time of maximum response to a test meal or at the 2-3 hour stage. Alternatively, careful caloric balance studies of a group of children of marriages of a diabetic and normal individual might reveal characteristic differences. If these children were followed in a longitudinal study, one might expect to observe the gradual appearance of a relative excess of the insulin antagonist in some. Finally, studies on the level of anti-insulins (and insulin) in the serum of primitive hunters and gatherers are called for, with the expectation of lower anti-insulin levels in

the primitives. With present assay techniques, observations concerning the correctness of these postulates are readily feasible. However, it seems likely that no matter what the mechanisms, the difference between predisposed and non-predisposed will be small and yield only to very precise techniques.

#### SOME EUGENIC CONSIDERATIONS

In recent years there have been numerous surmises concerning the nature of the genetic readjustments man must make to his rapidly changing environment. Genes and combinations of genes which were at one time an asset may in the face of environmental change become a liability. Perhaps the best documented illustration of this statement concerns the gene responsible for sickle cell hemoglobin. In regions hyperendemic for falciparum malaria, individuals heterozygous for this gene, with the sickle cell trait, possess a relative immunity to malaria which offsets from the population standpoint the early death of some homozygous individuals from sickle cell anemia (reviews in Allison, 1955, 1957; Rucknagel and Neel, 1961). But as malaria is controlled, the benefits conferred on populations by the possession of this gene will disappear, and only the negative aspects, i.e., sickle cell anemia, will be apparent to the inquiring medical mind. It seems quite likely we are witnessing a similar genetic readjustment with respect to the gene(s) responsible for the predisposition to diabetes. However, if the foregoing surmises are correct, the factors responsible for the altered selective value of the diabetic genotype are more complex than those concerned with sickle cell anemia, involving, as they may, changing dietary and exercise patterns, new types of stresses and altered reproductive patterns.

There may be a further parallelism between diabetes mellitus and sickle cell anemia. In the opening paragraph reference was made to the possibility of a very simple mode of inheritance of the predisposition to this disease, with several investigators suggesting the basis to be homozygosity for a single recessive gene. Thus far only the metabolic attributes of the predisposed individual, i.e., the homozygote, have been discussed. But what of the relatively many heterozygous gene carriers? It is a well established truism of genetics that genes when heterozygous discharge the same functions as when homozygous, but with less striking phenotypic effects. If the foregoing suggestions concerning the metabolism of the predisposed are correct, it follows that the heterozygote may also be a "thrifty" genotype, albeit to a lesser degree. Were this so, the advantage of the heterozygote might offset the interference with normal reproduction suffered by some homozygotes, and a "balanced polymorphism" very similar to that existing for the sickle cell gene would exist.

Should the foregoing thoughts prove correct, then diabetes underlines one of the ethical dilemmas of modern medicine. If the dietary and cultural conditions which elicit the relatively high frequency of diabetes in the Western World are destined to spread and persist over the entire globe, then, to the extent that modern medicine makes it possible for diabetics to propagate, it interferes with genetic evolution. But if, on the other hand, the mounting pressure of population numbers means an eventual decline in the standard of living with, in many parts of the world, a persistence or return to seasonal fluc-

tuations in the availability of food, then efforts to preserve the diabetic genotype through this transient period of plenty are in the interests of mankind. Here is a striking illustration of the need for caution in approaching what at first glance seem to be "obvious" eugenic considerations!

## SUMMARY

The problem of understanding the genetic nature of man is both a philosophical and, in these days of rapidly changing environment, a practical challenge. Progress demands both a broad approach on the theoretical level and a very specific approach geared to particular traits presenting favorable analytic opportunities. Diabetes mellitus may be one such trait. In this essay an hypothesis has been advanced which envisions diabetes mellitus as an untoward aspect of a "thriftness" genotype which is less of an asset now than in the feast-or-famine days of hunting and gathering cultures. Specific means of testing the hypothesis are suggested.

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