PREDIABETES

A Synthesis

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

Senior Lecturer, Department of Medicine, University of Cape Town, and Physician to Groote Schuur Hospital, Cape, South Africa

What It Is

Before you are born you are pre-natal, yet already in existence; before you are diabetic you are prediabetic—a state which is not normality nor yet a disease, but certainly there. This term 'Prediabetes' thus connotes the state of a person during the period before he or she becomes plainly and clinically diabetic, in which, however, there is a latent abnormality which may show itself under certain specific conditions. Since experts would not agree on the precise definition of 'Diabetes,' or on what constitutes an abnormal glucose tolerance curve, it is clearly impossible to define 'Prediabetes' more exactly. There are people without symptoms whose gross carbohydrate abnormality is discovered accidentally, but who everyone would agree are diabetic. Such people retain their carbohydrate disorder for the rest of their lives, and are not to be considered 'prediabetic'—their condition is better called mild asymptomatic 'chemical' diabetes. The existence of this phenomenon makes it impossible to know in retrospect just how long a new patient has been truly diabetic; in other words at what point her glucose tolerance became grossly impaired.

In Mothers

When, with improved treatment, the pregnancies of diabetic women came to term, it became plain that the newborn were often dead, and/or excessively large. Skipper,¹ 25 years ago, was possibly the first to observe that women may have big babies long before they developed overt diabetes. He and Priscilla White² (1935) both suggested that mothers who have large babies should be systematically examined for diabetes, but this was not done on any scale until quite recently.

Several writers from different parts of the world have since confirmed the high frequency of overweight babies (variously considered as over 9 lb., 10 lb., 4 or 4½ kilos) and of late foetal or neonatal death ('perinatal' loss).³⁻²⁰

There seems to be general agreement that the

perinatal loss in prediabetic years is around 15 to 20 per cent., rising to as high as 30 to 50 per cent. in the two to five years immediately preceding the diagnosis of diabetes. A few workers, however, have found no evidence for an increased foetal loss before the appearance of diabetes. Thus Pirart²¹ (in Brussels) observed no 'significant difference' from the general perinatal mortality in the past histories of 502 diabetic mothers, while Wilkerson²² (in Boston) has found only ten perinatal deaths in 182 pregnancies in women who had previously been diagnosed as prediabetic (i.e. in a 'prospective' study). It is possible that the latter's series was unlikely to contain mothers who had previously produced stillborn children; all the same the explanation of these discrepant findings is not clear.

As far as I am aware, there is universal agreement with regard to the tendency for large babies to be produced in prediabetic years, and furthermore that this tendency is plainly evident from the beginning of the childbearing age, and shows but little increase with the approach of overt diabetes. In our own series,¹⁶ the incidence of babies weighing over 10 lb. in the ten years immediately prior to the diagnosis of diabetes was 50 per cent. (by questioning), and was 35 per cent. in the period 20 to 29 years preceding the diagnosis.

Not all future diabetic mothers bear large babies or stillbirths, even if they have many children. (We found that 62 per cent. of mothers in their prediabetic years claimed to have produced at least one baby over 10 lb. at birth.) Furthermore, there is no apparent relation between gigantism and viability of the child; in fact there is some evidence that the smaller babies (of diabetic mothers) are less viable.²³ There does appear to be some tendency for one large baby to be followed by subsequent large babies, and sometimes for the birth weights to rise progressively, but these are not strict rules.¹⁸ Thus it is quite common for a 12 pounder to be followed by a 7 pounder and likewise for two or three stillbirths to be followed

FIG. 1.—Note that the proband's mother was diabetic, that she herself did not become diabetic until four years after her last child, and that even after so many stillbirths she can produce a stack of live children.

by a live child (Fig. 1). In other words this method of analysis yields evidence of only occasional progression in the abnormal or damaging prediabetic factors, whatever they may be.

Other, more controversial obstetric associations of prediabetes include infertility, miscarriage, toxæmia of pregnancy, hydramnios, prematurity, and congenital malformation in the foetus, and excessive lactation.

Miscarriage. Since the evidence is still unconvincing that miscarriages are more frequent than normal in established diabetics, it is to be expected that it is also uncertain with regard to prediabetics. Pirart²¹ finds no evidence of an increase. Nevertheless, on the assumption that repeated unexplained abortions might be a prediabetic or latent diabetic phenomenon, Williams,²⁴ Gilbert¹⁴ and Hoet²⁵ have performed glucose tolerance tests in the mothers, and frequently found them to be abnormal.

Toxæmia of pregnancy. Much the same position exists here as with repeated abortions—we are uncertain of the true relationship to diabetes or prediabetes. Again Pirart²¹ finds no increase.

Hydramnios. There can be no doubt that hydramnios is a very frequent concomitant of the diabetic pregnancy. Its incidence in prediabetes has not yet been elucidated.

Prematurity. There is little if any tendency for the diabetic's baby to be born prematurely; neither is the large infant of a diabetic post-mature²⁶—it actually behaves more like a premature.

Congenital malformations. This is an important subject on which there is no unanimity of opinion. With regard to diabetics' children, several reports

have been published for and against the existence of a high anomaly rate. P. White²⁷ states that malformations 'have occurred in 80 per cent. of the infants of our diabetic mothers, compared with the expected incidence of 1.8 per cent. (sic)'. The precise derivation of these figures is, however, rather uncertain. Recent careful analyses by Cardell²⁶ (on autopsy material) and Farquhar²⁸ (in live children and their families) have indicated that there is no excessive anomaly rate in the offspring of diabetics. Hoet *et al.*²⁸ claim to have found a distinctly abnormal glucose tolerance curve in 22 per cent. of the mothers of 50 children with severe congenital malformation.

Diabetes occurring during pregnancy. It can now be categorically stated that glucose tolerance is not impaired in a completely normal person during pregnancy, or that any impairment is so slight as to be unimportant (Jackson,¹⁶ Hagen²⁹ and unpublished data). Consequently an apparently 'temporary' diabetic state or significant impairment of sugar tolerance during pregnancy indicates a state of potentially permanent diabetes in the mother. In such a case the pregnancy has brought to light the prediabetic state. This is frequently further indicated by the resulting foetus being large or stillborn. Sometimes a gross clinical diabetic state, even with ketosis, may appear during gestation, yet the patient, and even her tolerance curve, may be normal after parturition (Fig. 2).

Excessive maternal weight gain. It is commonplace for women to start gaining weight excessively during or soon after pregnancy. This tendency may be exaggerated in those who later become diabetic.^{3, 13, 30}

FIG. 2.—After this young woman had been in diabetic ketosis in late pregnancy, her carbohydrate metabolism appeared to revert completely to normal, though a subsequent pregnancy and the use of the cortisone glucose tolerance test revealed the latent diabetic trait. (Glucose tolerance curves with half-hourly readings are shown.)

In Fathers

It has been demonstrated^{16, 21, 31} that diabetic and prediabetic men father, on the whole, larger babies than do non-diabetics. This larger size of men's babies is by no means as striking as in the case of mothers (31 per cent. of babies of prediabetic mothers were over 10 lb. in my series, 10.7 per cent. of (pre)diabetic fathers and 3.7 per cent. of normal parents). On the other hand, the presence of diabetes in the father had no ill effect on foetal survival.

In Families

Diabetes is certainly hereditary and generally believed to be inherited through a common, autosomal recessive gene. In view of the frequency of the gene, a parent-child inheritance will often appear clinically (unlike the case in rarer recessive diseases). Roughly 20 per cent. of children with an affected parent may expect to become diabetic themselves.²⁷ Possibly there is more chance of developing diabetes if one has a diabetic mother than a diabetic father.³² Prediabetes can therefore be suspected in anyone with a strong family history, and must actually be considered to be present in certain specific instances, as when an identical twin or both parents are diabetic.

In Patients with Obesity

Whether obesity predisposes to diabetes, or whether the prediabetic abnormality predisposes to the development of obesity (? through increasing appetite), or whether both things happen, is incompletely known. Certainly obesity is excessively common in the diabetic clinic, mild diabetes is ameliorated or even clinically abolished by reduction in weight,³³ and several workers have found a high rate of abnormal glucose tolerance in unselected obese patients, especially if they had been obese for a long time (static obesity).^{34, 35} A strain of obese mice become mildly diabetic unless their food intake is restricted³⁶ while some partially pancreatectomized animals may be made diabetic if they are overfed.³⁷ On the whole it would appear as if obesity, by increasing the total body mass and so the total metabolic turnover for which insulin is necessary, will expose those pancreases whose reserve is insufficient to meet such extra demands. After reduction in body weight, the pancreas may again become adequate for more normal demands, and the 'diabetes' thus remits.

The 'Temporary Diabetes' Related to Certain Other Stresses

It is well known that there is a high incidence of

temporarily diminished sugar tolerance and even gross diabetes in patients suffering from acromegaly, Cushing's syndrome, hyperthyroidism, severe fractures, severe burns, staphylococcal or other infections, undergoing treatment with glucocorticoids or even after such a condition as myocardial infarction. When investigations have been made, it has been found that there is a high incidence of diabetes in the families of persons so affected.^{38, 39} It seems likely that the particular condition in each case simply renders overt a latent or pre-diabetic state.

What it does to the Foetus^{26, 40}

The diabetic's baby is generally abnormal in several ways. It is overlarge, fat, rubicund and oedematous-looking (pitting oedema is not usual, however). Many of its organs are large, in particular the liver, heart, and islets of Langerhans. The ovaries frequently contain luteal cysts and luteinised follicles.⁴¹ Active extramedullary haematopoiesis is usual, even in the full term infant, and the haematocrit reading is sometimes very high. The infant, even though large, behaves like a weak premature; it respires with difficulty, sucks poorly, easily regurgitates fluid into its lungs and is liable to hyaline membrane disease. Hypoglycaemia is probably more extreme and longer lasting than in other infants,²³ but is now generally believed to cause no harm to the baby.

We believe that most, and probably all of these abnormalities may also occur in the foetus of the prediabetic. Most interesting to us have been the islets of Langerhans. Van Beek⁴² was the first to insist that enlarged islets in a stillborn foetus meant diabetes or potential diabetes in the mother. Woolf and I⁴³ have confirmed this. We have found the proportion of islet tissue in the pancreas of the prediabetic's foetus to be about 7 per cent., as against about 1.3 per cent. in other foetuses. Furthermore the islets appeared to contain a higher proportion of β cells than normal, and the β cells were unusually full of staining granules. This would seem to indicate a very high insulin content of such a pancreas—even 30 times the normal.

The question of congenital anomalies is vexed, as mentioned above. Hoet²⁸ is most insistent that the *prediabetic* state accounts for many severe congenital anomalies (some 30 per cent. in fact) but this has not been confirmed.

Likewise no general agreement has been reached regarding the usual state of the diabetic woman's placenta. It is frequently stated to be heavier than normal and to show advanced arteriosclerotic and 'aging' changes and infarction.^{39, 40} Recent investigators,^{26, 53} however, have been unable to find any significant difference from the placenta of

a normal mother. Consequently there are no good pathological grounds for suggesting that any foetal abnormalities are produced by an abnormal placenta.

Causation of the Embryopathy

The first and obvious idea as to the cause of the foetal abnormalities was that the maternal hyperglycaemia allowed increased growth and perhaps in some other way damaged the developing foetus. However, the same sort of embryopathy occurs in the prediabetic, in whom no hyperglycaemia can be demonstrated at all. This theory must then fall away.

The next hypothesis concerned growth hormone. Young⁴⁵ and his co-workers have shown that growth hormone could make dogs permanently diabetic, that it was in fact the so-called diabetogenic hormone of the pituitary, and that it appeared to stimulate the islets of Langerhans to hypertrophy before the diabetes became severe, after which degenerative changes appeared in the β cells. The known pituitary hyperplasia in pregnancy, combined with the hyperplastic pregnancy pancreas and the large size of the diabetic's baby, all seemed to fit in very nicely with the idea of excessive growth hormone stimulation in diabetic pregnancy. Abaza, Varoud-Vial and Rombauts⁴⁶ actually described the 'Syndrome de Young,' consisting of prolonged growth in women, high foetal mortality, large babies, hyperlactation, obesity and diabetes. Then Hultquist and Engfeldt⁴⁷ reported the development of oversized foetuses in experimental animals given growth hormone during pregnancy, and the theory began to seem plausible. Against it, however, was the absence of acromegaloid features in the pregnant diabetic, the infrequency of diabetes in human acromegaly and—most damning—the absence of particularly heavy babies or foetal deaths in the acromegalic pregnancy.³⁸ Furthermore growth hormone activity is associated with nitrogen retention rather than fat, and the muscles of the diabetic's baby are fat and flabby. Then no one has been able to confirm Hultquist's work; in fact such fine experimentalists as Jost⁴⁸ have produced only negative evidence. Until we can measure circulating growth hormone, the question of its participation in this syndrome is likely to remain in doubt.

That corticotropin and the adrenal glucocorticoids can also act as diabetogenic agents there is no doubt. Against the rather impressive relationship of glucocorticoids to diabetes and diabetic pregnancy are (1) the almost invariable failure to produce any similar embryopathy experimentally, (2) the fact that babies born to

mothers with Cushing's syndrome are neither large nor dead (series collected by the author) and (3) the absence of any excessive rise in plasma cortisol level during pregnancy in a diabetic.^{49, 50} In our series we actually found a lower mean maximum level of cortisol in diabetic and pre-diabetic pregnant women than in the non-diabetic group. At the moment we can only say that the part played by glucocorticoids in diabetic embryopathy is uncertain.

What of insulin itself in this syndrome? Is it not tempting to think that those large islets play some part? Insulin is a growth hormone;^{51, 52} in fact pituitary growth hormone will not function without insulin. It seems possible that the abnormal size of the foetus might be due to foetal insulin activity; but this would still leave unsolved the other features, and also the actual cause of the enlarged islets themselves.

Other suggestions have been made; e.g. anoxia,⁵³ abnormal placenta (discussed above). White²⁷ believes that a sex hormonal imbalance occurs in diabetic pregnancies, and she claims not only an improved live birth rate, but also a reduction in foetal size, by treatment with large doses of oestrogens and progesterone. Obesity in the mother may play a small part in some cases, since it has been shown that, on the whole, the larger the mother, the larger the infant.^{16, 18} The role of maternal obesity, however, can be only a very small one. Heredity may also have some small place in the production of big babies, as indicated by the studies on diabetic fathers (discussed above) and the work of Penrose⁵⁴ on the inheritance of large-size infants in non-diabetic families.

Relationship between different parts of the embryopathy. Although the progeny of diabetics and prediabetics are often large or dead, there is no close relationship between oversize and perinatal mortality. Hoet claims further that the congenital anomalies in the babies of the pre-diabetic occur quite independently of gigantism or perinatal mortality (except of course where the anomaly itself is lethal).

This makes one wonder whether the factors responsible for the gigantism are not quite different from those which cause the stillbirth (or the congenital anomalies).

Malins⁵⁵ has observed an interesting relationship between the diabetogenic effect of pregnancy in the mother with established diabetes and the survival of the infant. He found that the foetus was less likely to survive in those cases where the mother needed a considerable increase in insulin dosage during pregnancy, and particularly where this higher insulin dose had to be continued after parturition.

What it Portends

The prediabetic state appears to extend back indefinitely into a woman's obstetrical past,^{16, 21, 56} its manifestations being limited only by the age of commencement of childbearing. Thus women whose diabetes is discovered when they are 70, may have a history of large babies and even stillbirths going back 30 or 40 years, although it is generally agreed that the foetal loss is particularly high in the five to ten years immediately preceding overt diabetes. Evidence for the existence of the prediabetic state in early life can be obtained from other quarters. Thus White²⁷ has found an alarmingly high proportion of abnormal glucose tolerance curves in young children of both diabetic mothers and diabetic fathers. It is plain that the great majority of these children will not become obvious diabetics until late in life (if they do so at all), yet they already manifest an underlying defect in their carbohydrate metabolism.

From this and evidence discussed elsewhere³⁸ it may be postulated that the underlying abnormal diabetic state exists from an early age (Fig. 3a), perhaps from birth, even when clinical diabetes does not appear until much later, and sometimes maybe not at all.

Further it seems reasonable to consider that diabetic vasculopathy is truly a part of diabetes;⁵⁷ that a potential diabetic inherits not only a congenitally defective pancreas but also defective blood vessels, particularly in certain sites, though it may equally well be that the sub-clinical pancreatic defect has itself a deleterious effect on blood vessel walls, long before diabetes becomes manifest. Certainly, then a poorly controlled diabetic increasingly damages his already defective vasculature, while careful control helps partially to protect it from further deterioration. If this is true one could not in fact expect insulin or other means of 'control' of diabetes *entirely* to prevent vascular disease since the vessels are already damaged by the time the diabetes is diagnosed.

Is Pregnancy Diabetogenic?

Pregnancy (and other 'stressing' factors mentioned above) can plainly be considered as at least temporarily diabetogenic to the mother (Fig. 2). Thus it usually worsens hyperglycaemia and retinopathy in an established diabetic, it may produce retinopathy for the first time, which disappears after parturition,^{58, 59} it causes hypertrophy in a normal woman's pancreas, it diminishes glucose tolerance in some apparently normal subjects, and it may potentiate the diabetogenic effect of cortisone or alloxan in laboratory animals.⁶⁰ The question of importance is whether the diabetogenic action has a permanent effect—in other words whether pregnancy predisposes to the

A CONCEPT OF DIABETES

FIG. 3a.—'Iceberg' conception of diabetes: most of it is below the clinical level of overt manifestations, which here include embryopathy at the age of 24, transient hyperglycaemia during staphylococcal infection and while on cortisone therapy, and clinically apparent diabetes at age of 45, with retinopathy and nephropathy at age of 55.

appearance, or earlier appearance, of clinical diabetes (Fig. 3b).

Suggesting that pregnancy is truly diabetogenic is the evidence that the incidence of diabetes is higher in married women than single,^{61, 62} that it rises with increasing parity,⁶³ and that it is very high among women who have borne ten or more children.⁶⁴ The latter author actually claimed that over 50 per cent. of such women became diabetic in his series. If this can be confirmed it would indicate that multiple pregnancies are diabetogenic even in the originally entirely normal (non-prediabetic) woman. However, another effect should also be evident, namely the age of onset of diabetes should be lower with increasing parity. This has not been found.⁶³

Next we must enquire whether pregnancy is diabetogenic for the child in the presumed abnormal internal environment of a diabetic or prediabetic mother. One certainly wonders whether the grossly hypertrophied islets of Langerhans in the infant should not suggest permanent damage. If this is so then the children of diabetic mothers should have a greater tendency to diabetes than the children of diabetic fathers. On the whole, however, it looks as if the abnormal diabetic or prediabetic maternal environment may produce acute damage to the foetus, or even death in utero, but that a surviving child usually recovers completely.

Summary of Implications of Prediabetes

Diabetes is certainly hereditary (generally

considered largely to be a Mendelian recessive characteristic). From this alone, as Conn⁶⁵ has pointed out, it might be stated that a diabetic presenting at 60 must have had the diabetic 'diathesis' all her life. Prediabetes, however, implies more than this. It suggests that some of the actual effects of the underlying condition are being produced before the clinical state is apparent, and that perhaps even the blood vessels are being damaged from an early age (Fig. 3a). I have suggested³⁸ that diabetes should be considered as starting at birth (if not before), though we cannot detect it till much later because of the crudeness of our yardstick of blood sugar level.

How to Diagnose it

Suspicion

The discussion in the first part of this paper will have indicated those people who may be suspected of being prediabetic. The hints are:

1. Positive family history, especially if close relatives are affected, and especially if a child develops diabetes under the age of 6.⁶⁶
2. Overlarge babies (especially if repeated).
3. Perinatal mortality (especially if repeated).
4. ? Repeated miscarriages; repeated pregnancy toxæmia.
5. ? Severe congenital anomalies in the child.
6. Obesity, ? especially when developing rapidly after pregnancy.
7. 'Temporary diabetes' during any acute stress.
8. Glycosuria during pregnancy, which should

IF PREGNANCY IS DIABETOGENIC

EACH PREGNANCY BRINGS THE SUBCLINICAL "PREDIABETES" NEARER TO THE CLINICAL LEVEL. SO THAT DIABETES WHICH WOULD HAVE APPEARED AT 60, OCCURS AT 45. ? DOES THIS HAPPEN.

FIG. 3b.—Should 3a really be drawn like this? If pregnancy is truly diabetogenic, each one will bring overt diabetes nearer, so altering the line of progression of the prediabetic state.

not be too readily shrugged aside as caused by a low renal threshold.

9. Xanthosis and mild carotinoderma.²⁸
10. Repeated attacks of acute pancreatitis.
11. Certain other conditions known to be frequently associated with mild diabetes, e.g. cancer of body of uterus, gout.⁶⁷
12. Renal glycosuria⁶⁸ or spontaneous (noninsulinomatous) hypoglycaemia ('dysinsulinism' of Harris.⁶⁹)⁷⁰
13. Typical diabetic-type vascular disorder (e.g. retinal aneurisms, or angina pectoris in a premenopausal woman).

Use of the Ordinary Glucose Tolerance Test

Since 1952, the results of several series of oral glucose tolerance tests in suspected prediabetics have been reported.^{16, 19, 21, 22, 71, 72} Of course a number of previously unsuspected, definite diabetics have been discovered, whose sugar tolerance curve no one would deny as being grossly abnormal. Some were found without glycosuria, even during pregnancy, despite blood sugar levels in the three hundreds. Such symptom-free, aglycosuric individuals might be considered 'prediabetic' in a sense. Presumably they should be treated as established diabetics, though the urine tests will be useless for control. I do not know of any follow-up studies in such cases.

Most controversy has centred around those

tolerance curves which have been just outside the authors' accepted normal limits. It has been found that the usual abnormality is a slightly high figure 2 or 2½ hours after the ingestion of glucose. In our own investigations we considered as abnormal a two-hour level above 140 mg. per 100 ml., with anything between 120 and 140 as 'suspicious' (capillary blood, 50 g. glucose, and modified Hagedorn-Jenson glucose estimation). Occasionally the 2- to 2½-hour level was normal, while the fasting level was just over 120 mg., or the 1-hour level above 200 mg. Such curves were also considered abnormal, but were much less common. Other workers, though using different techniques, have accepted very similar criteria of abnormality.

Series with adequate controls have demonstrated a statistically significant increase in abnormal curves in women who gave rise to stillbirths (especially stillbirths with large islets of Langerhans), to large babies, or who had glycosuria during pregnancy, or in men or women with diabetes in their families. Despite this, and the rather remarkable constancy of the abnormalities on repetition of the test, many authorities at first would not believe that such minor changes in tolerance as shown by 2- or 2½-hour levels could be meaningful.⁷³ The validity of such a belief, however, has since been vindicated by follow-up studies which have demonstrated the appearance of overt diabetes in many of those whose earlier

tolerance curves had been so slightly abnormal.^{22, 65, 74, 75}

It must not be supposed that abnormal curves will be found in the majority of women who have produced large babies or stillbirths. For one thing prediabetes or diabetes is only one cause of these phenomena, and secondly many women, even though prediabetic, may have completely normal tolerance curves, especially if they are tested when not pregnant. It seems quite probable that the minor abnormalities in tolerance of 'prediabetic' type are to be found chiefly within the five-year period before overt diabetes appears, so that patients who are tested in an earlier prediabetic phase may show no abnormality in glucose tolerance.

From what has been said above it is plainly advantageous to perform repeated tolerance tests during pregnancy, whenever possible. Abnormalities are more likely to be found then, and are significant.

The Cortisone (augmented) Glucose Tolerance Test

Berger (in 1952)⁷⁶ used corticotropin (ACTH) to 'sensitise' the glucose tolerance test, and Fajans and Conn,⁷⁷ in 1954, reported results using cortisone for the same purpose. They investigated 152 healthy relatives of diabetic patients and found 19 per cent. of these to be unknown diabetics, as against 1 of 50 control subjects. They then tested 75 non-diabetic relatives of diabetics by cortisone/glucose tolerance test and found significant impairment in 24 per cent., as against 1 of 37 normal controls. They further demonstrated that six patients whose carbohydrate tolerance had apparently reverted to normal after losing weight nevertheless gave a positive response to the test when this was augmented with cortisone. It appeared, therefore, that two distinct groups of reactors to this test existed, and that a high proportion of positive reactors occurred in the relatives of diabetics. Were these people really prediabetics—the ones who would later themselves become diabetic? So far four out of 30 of such abnormal reactors who have been followed up have become grossly diabetic.⁶⁵

West,⁷⁸ with similar but somewhat modified techniques, confirmed the basic conclusion of Fajans and Conn. We have continued with Fajan's technique the testing of certain special groups of patients (as yet unpublished data). Our tentative results so far obtained may be numbered:

1. The mean rise in tolerance curve in apparently normal people over 45 is higher than in those under 45 (confirming West's finding).
2. The mean rise in normal pregnant women is higher than in non-pregnant controls.

3. A proportion of mild diabetics show no rise at all after cortisone.
4. A high proportion of patients who are almost certainly prediabetic (on obstetric grounds and/or on account of both parents or an identical twin being diabetic) give negative responses.

It would therefore appear that this test, while of some value in indicating the potential diabetic (Fig. 2), frequently fails to do so, while in older people or during pregnancy it may appear falsely positive unless the levels considered to be abnormal are raised.

Duncan⁷⁹ gives reasons for preferring to use intravenous glucose tolerance tests, with the change in increment index being the single-figure criterion of abnormality. He found a positive response in all mild diabetics and latent diabetics, and in 9 out of 19 suspected prediabetics. This would appear to be a more sensitive method of detecting prediabetes.

From the Pancreas of the Stillborn

As discussed above, the islet hyperplasia in the pancreas of stillborn infants is characteristic of erythroblastosis, diabetes or prediabetes in the mother. If Rh incompatibility can be excluded then it is extremely likely (? virtually certain) that the mother is diabetic or prediabetic. Woolf and Jackson⁴⁸ followed up 12 mothers whose stillborn infants had shown islet hyperplasia, without there being Rh incompatibility or maternal diabetes at the time of the pregnancy. Eight of these 12 are now plainly diabetic, and three others show abnormal glucose tolerance curves of 'prediabetic' type. The final mother still has normal glucose and cortisone/glucose tolerance curves, yet is almost certainly prediabetic, since apart from her highly suspicious obstetric history both her parents are diabetic. It seems legitimate to conclude, therefore, that the finding of grossly enlarged islets in a stillborn is a very good way of diagnosing prediabetes in the mother, provided only that erythroblastosis can be ruled out.

A corollary of these conclusions is pointed out by Jackson and Woolf,⁸⁰ namely that from the point of view of the morbid anatomist, a number of stillbirths for whom no adequate cause of death can be found, must be associated with prediabetes in the mother. The findings of large islets on autopsy, then, would at least provide a partial explanation, and a new category, for these unexplained stillbirths.

For the assessment of the size of pancreatic islets (as a proportion of total pancreatic tissue) accurate methods are available,^{43, 81, 82} which indicate that the mean normal proportion is a 1 to 2 per cent. of total pancreas, while the

'prediabetic' proportion is 4 to 15 per cent. In general, however, the enlargement of the islets is quite obvious on inspection, so that the term 'continents' may be more suitably applied to them.

Follow-up

Plainly the final method of diagnosis of prediabetes is to follow up the individual until she becomes obviously diabetic. As indicated above this has now been done by several workers.

What Can We Do About It ?

The study and diagnosis of prediabetes is not of academic interest only. It is helping us to understand the meaning and natural history of diabetes, some aspects of its genetics, where best to look in a search for new diabetics, factors in the development of the overt disease, the importance of so-called 'temporary' diabetes, and the cause of certain stillbirths. From the point of view of the patients, can its diagnosis be of value in prophylaxis ?

Prophylaxis During Subsequent Pregnancies

Having seen the weak, oversized, Cushingoid babies of some of our prediabetics, and bearing in mind their tendency to stillbirth and birth injury and the improved results now being obtained by modern management of the diabetic's parturition, I have no hesitation in recommending similar management in the case of the prediabetic. In other words the pregnancy should be terminated around the 36th to 37th week by surgical induction provided the foetus is believed to be of sufficient size. In certain circumstances Caesarean section should be resorted to. The newborn infant should be treated precisely as though the mother were a severe diabetic, with extra care in handling, oxygen tent, stomach aspiration, temperature control and no food for 48 hours. With these simple measures we have so far had complete success in prediabetics whose previous infants had been stillborn, though our results are insufficient to be statistically valid (see also Carrington *et al.*²⁰).

Hoet goes further,²⁸ and uses insulin during pregnancy in his suspected prediabetics, even though there is no real hyperglycaemia. His dosage rises during the course of gestation to 60 or 80 units daily—according to the mother's tolerance. He claims to prevent miscarriages, stillbirths and congenital malformations.

Wilkerson's figures²² appear to show that insulin (20 units per day) during pregnancy in suspected prediabetics will reduce the mean birthweight of the infants. In controlled series, 25 babies out of 182 were over 9 lb. when the mother was untreated, as against 8 out of 162 in the maternally treated group.

Prophylaxis against Future Diabetes, in Mother and Child

The most obvious abnormality to treat in many prediabetics is obesity. A diet of 800 calories a day of thereabouts is frequently necessary. If loss in weight is sufficient to prevent the onset of overt diabetes it is not unreasonable to believe that it also at least delays the vascular degeneration.

The actual diet to be recommended to prediabetics in general is controversial at the present time. Perhaps they, par excellence, should have a low saturated fat intake.

Hoet and Wilkerson hope that insulin given during pregnancy may also delay or prevent the onset of diabetes in the mother, and decrease the chance of diabetes occurring in the children. The latter possibility, of course, can apply only if the maternal prediabetic intrauterine environment really does predispose to diabetes in the infant.

An obvious eugenic point might be mentioned here. It would seem plainly inadvisable for two diabetics to marry each other, or for a diabetic or prediabetic to marry into a family with several diabetic members. What with mixed diabetic clinics, camps for diabetics, the prolificity of the mild and treated diabetic, and the improved foetal salvage, the incidence of diabetes must surely be increasing.

Concluding Remarks

We are really only on the fringe of knowledge and understanding of the fascinating state of prediabetes. It is significant that the Public Health authorities (e.g. Wilkerson) have recognized its importance and entered its field of research. If our appreciation of the condition seems fragmentary at present, it must be realized that it is difficult to grapple with a disease which is not there.

Acknowledgements

I should like to thank the innumerable people who have discussed this subject with me, all of whom cannot be mentioned. Professor G. C. Linder, Dr. B. Lewis and Dr. N. Woolf have been particularly associated with me in our own work. I acknowledge the great help of Mrs. E. Orkin and Dr. R. Hoffenberg with the manuscript.

Figures 2 and 3a are reproduced by permission of the Editor of *The Lancet*.

REFERENCES

1. SKIPPER, E. (1933), *Quart. J. Med.*, **2**, 353.
2. WHITE, P. (1935), *Surg. Gynec. Obstet.*, **61**, 324.
3. ALLEN, E. (1939), *Amer. J. Obstet. Gynec.*, **38**, 98.
4. MENGERT, W. F., and LAUGHLIN, K. A. (1939), *Surg. Gynec. Obstet.*, **69**, 615.
5. MILLER, H. C., HURWITZ, D., and KUDER, K. (1944), *J. Amer. Assoc.*, **124**, 271.
6. MILLER, H. C. (1945), *New Engl. J. Med.*, **233**, 376.
7. PALMER, L. D., and BARNES, R. H. (1945), *West. J. Surg.*, **53**, 195.

8. HENLEY, W. E. (1947), *N.Z. med. J.*, **46**, 386.
9. WHITE, P. (1947), *Penn. med. J.*, **50**, 705.
10. KRISS, J. P., and FUTCHER, P. H. (1948), *J. clin. Endocr.*, **8**, 380.
11. BARNES, H. H. F., and MORGAN, M. E. (1949), *Brit. med. J.*, **1**, 51.
12. PATTERSON, M., and BERNSTEIN, N. (1949), *Arch. intern. Med.*, **83**, 390.
13. GILBERT, J. A. L., and DUNLOP, D. M. (1949), *Brit. med. J.*, **1**, 48.
14. GILBERT, J. A. L. (1949), *Ibid.*, **1**, 702.
15. MOSS, J. M., and MULHOLLAND, H. B. (1951), *Ann. intern. Med.*, **34**, 678.
16. JACKSON, W. P. U. (1952), *Brit. med. J.*, **2**, 690.
17. JACKSON, W. P. U. (1953), *S. Afr. med. J.*, **27**, 795.
18. PIRART, J. (1954), *Ann. Endocr. (Paris)*, **15**, 58.
19. CARRINGTON, E. R., SHUMAN, C. R., and REARDON, H. S. (1957), *Obstet. Gynec.*, **9**, 664.
20. CARRINGTON, E. R., REARDON, H. S., and SHUMAN, C. R. (1958), *J. Amer. med. Ass.*, **166**, 245.
21. PIRART, J. (1955), *Acta. Endocr.*, **20**, 192.
22. WILKERSON, H. L. G., and REMEIN, Q. R. (1957), *Diabetes*, **6**, 324, and personal communication.
23. FARQUHAR, J. (1958), personal communication.
24. WILLIAMS, E. C. P. (1953), *Lancet*, **ii**, 859.
25. HOET, J. P., and BRASSEUR, L. (1954), *Ann. Endocr. (Paris)*, **15**, 26.
26. CARDELL, B. S. (1953), *J. Obstet. Gynaec. Brit. Emp.*, **60**, 834.
27. ROOT, H. F., and WHITE, P. (1956), 'Diabetes Mellitus.' Landsberger Medical Books, New York.
28. HOET, J. J., GOMMERS, A., and HOET, J. P. (1958), 3rd Congress of International Diabetes Federation, Dusseldorf, July 24.
29. HAGEN, A. (1958), *Ibid.*
30. SHELDON, J. H. (1949), *Lancet*, **ii**, 869.
31. JACKSON, W. P. U. (1954), *J. clin. Endocr.*, **14**, 177.
32. BOULIN, R. (1958), 3rd Congress of International Diabetes Federation, Dusseldorf (*Lancet*, **ii**, 314).
33. NEWBURGH, L. H., and CONN, J. W. (1939), *J. Amer. Ass.*, **112**, 7.
34. OGILVIE, R. F. (1935), *Quart. J. Med.*, **4**, 345.
35. BEAUDOIN, R., VAN ITALLIE, T. B., and MAYER, J. (1953), *J. Clin. Nutr.*, **1**, 91.
36. MAYER, J., RUSSELL, R. E., BATES, M. W., and DICKIE, M. M. (1953), *Metabolism*, **2**, 9.
37. FOGLIA, V. G. (1944), *Rev. Soc. argent. Biol.*, **20**, 21.
38. JACKSON, W. P. U. (1955), *Lancet*, **ii**, 625.
39. JOSLIN, E. P., ROOT, H. F., WHITE, P., and MARBLE, A. (1952), 'The Treatment of Diabetes Mellitus,' 9th ed., Philadelphia.
40. WARREN, S., LE COMPTE, P. M. (1952): 'The Pathology of Diabetes Mellitus, 3rd ed., Philadelphia.
41. AHLVIN, R. C., and BAUER, W. C. (1957), *J. Dis. Child.*, **93**, 107.
42. VAN BEEK, C. (1952), at 1st International Congress of International Diabetes Federation, Leyden, Holland.
43. WOOLF, N., and JACKSON, W. P. U. (1957), *J. Path. Bact.*, **74**, 223.
44. REIS, R. A. (1958), 3rd Congress of International Diabetes Federation, Dusseldorf, July 24.
45. YOUNG, F. G. (1951), *Brit. med. J.*, **ii**, 1167.
46. ABAZA, A., VARROUD-VIAL, J., and ROMBAUTS, M. (1953), *Presse med.*, **61**, 495.
47. HULTQUIST, G. T., and ENGFELDT, B. (1949), *Acta. Endocr. (Kbh.)*, **3**, 365.
48. JOST, A. J., and PICON, L. (1957), *Symp. Soc. exp. Biol. N. Y.*, **11**, 228.
49. LITTLE, B., VANCE, V. K., and ROSSI, E. (1958), *J. clin. Endocr.*, **18**, 49.
50. JACKSON, W. P. U., and LEWIS, B., unpublished data.
51. BEST, C. H. (1953), *Ann. intern. Med.*, **39**, 433.
52. YOUNG, F. G. (1953), *Recent Progr. Hormone Res.*, **8**, 471.
53. PEEL, J. H. (1958), 3rd Congress of International Diabetes Federation, Dusseldorf, July 24.
54. PENROSE, L. S. (1952), *Ann. Eugen. (Camb.)*, **16**, 378.
55. MALINS, J. (1958), 3rd Congress of International Federation, Dusseldorf, July 24.
56. FUTCHER, P. H., and LONG, N. W. (1954), *Bull. Johns Hopk. Hosp.*, **94**, 128.
57. DOLGER, H. (1947), *J. Amer. med. Ass.*, **134**, 1289.
58. BECKER, B. (1952), *Ann. intern. Med.*, **37**, 273.
59. LAWRENCE, R. D. (1948), *Brit. J. Ophthalm.*, **32**, 461.
60. HOET, J. P. (1954), *Diabetes*, **3**, 1.
61. MOSENTHAL, H. O., and BOLDUAN, C. (1933), *Amer. J. med. Sci.*, **186**, 605.
62. JOSLIN, E. P., DUBLIN, L. I., and MARKS, H. H. (1936), *Ibid.*, **191**, 759; and (1937), **193**, 8.
63. PYKE, D. A. (1956), *Lancet*, **i**, 818.
64. MURPHY, R. (1957), *Conn. St. med. J.*, **21**, 306.
65. CONN, J. W. (1958), Banting Memorial Lecture, 18th Annual Meeting American Diabetic Association, June 21.
66. HOET, J. P. (1957), Symposium on 'Chronic Disease' (WHO), Amsterdam, Sept.-Oct.
67. WEISS, T. E., SEGALOFF, A., and MOORE, C. (1957), *Metabolism*, **6**, 103.
68. FAJANS, S. (1958), personal communication.
69. HARRIS, S. (1924), *J. Amer. med. Ass.*, **83**, 729.
70. SELTZER, H. S., FAJANS, S. S., and CONN, J. W. (1956), *Diabetes*, **5**, 437.
71. KRITZER, M. D. (1952), *Med. Clin. N. Amer.*, **36**, 1151.
72. LUND, C. J., and WEESE, W. H. (1953), *Amer. J. Obstet. Gynec.*, **65**, 815.
73. *Brit. med. J.*, (1952), **ii**, 712.
74. MCCULLAGH, E. P., FAWELL, W. N., and LANE, F. J. (1954), *J. Amer. Ass.*, **156**, 925.
75. JACKSON, W. P. U., and WOOLF, N. (1957), *Lancet*, **i**, 614.
76. BERGER, H. (1952), *J. Amer. med. Ass.*, **148**, 364.
77. FAJANS, S. S., and CONN, J. W. (1954), *Diabetes*, **3**, 296.
78. WEST, K. M. (1957), *Diabetes*, **6**, 168.
79. DUNCAN, L. J. P. (1956), *Quart. J. exper. Physiol.*, **41**, 453.
80. JACKSON, W. P. U., and WOOLF, N. (1958), *Diabetes*, **7**, 446.
81. CARDELL, B. S. (1953), *J. Path. Bact.*, **66**, 335.
82. McLEAN, N., and OGILVIE, R. F. (1955), *Diabetes*, **4**, 367

RUTHIN CASTLE, NORTH WALES

A Clinic for the diagnosis and treatment of Internal Diseases (except Mental or Infectious Diseases). The Clinic is provided with a staff of doctors, nurses, technicians, modern Radiological and Physiotherapy departments.

The surroundings are beautiful. The climate is mild. There is central heating throughout. The annual rainfall is 30.5 inches, that is less than the average for England.

The Fees are inclusive and vary according to the room occupied.

For particulars apply to THE SECRETARY, Ruthin Castle, North Wales.

telegrams: Castle, Ruthin

Telephone: Ruthin 66