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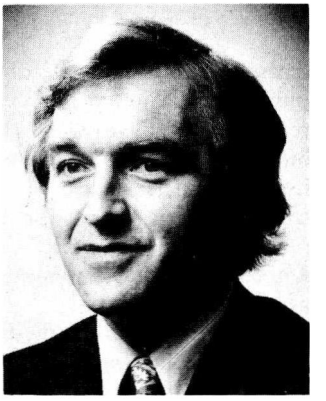

Foreword

This issue is not intended as a comprehensive textbook of diabetes — many excellent ones are already available. Its aim is to highlight significant basic and therapeutic advances over the past five years in the burgeoning field of diabetes research.

Throughout the world diabetes is being increasingly recognized as a major public health problem and the establishment in the U.S.A. of a National Commission on Diabetes is a milestone which should lead other governments to recognize their responsibilities in solving the problems which it poses.

All major public health victories of the past century have been brought about by prevention, and this must be the ultimate aim of diabetes research. Unfortunately, the belated recognition that diabetes is a syndrome has made the task of dissecting out its aetiologies and pathogeneses more difficult. That an inherited susceptibility exists in juvenile onset diabetes is clearly shown by its association with the HLA antigens, but equally important from the point of view of prevention is the identification of the environmental factors which trigger beta cell destruction. In spite of a bewildering variety of animal models of diabetes, we still need to find out how the beta cell of the *human* diabetic is abnormal, a task hampered by the inaccessibility of the pancreas. There is still a need for more basic research on the growth and replication of human beta cells and the process of synthesis and secretion of insulin.

The place of hormones other than insulin in the aetiology and course of diabetes remains speculative. Such disturbances as have been shown appear to be the consequences of insulin deficiency. The discovery of somatostatin has provided an exciting research tool, although any clinical application awaits modification of the molecule to make it more selective.

From the stand point of the consumer, the diabetic patient, the past five years have been disappointing.

On the credit side there have been two important advances in treatment. The introduction of low dose insulin regimes has improved and simplified the treatment of ketoacidosis, although mortality remains high in those past middle age. Secondly, photocoagulation has been shown to be effective in preserving vision in patients with maculopathy or new vessels on the disc. Furthermore, the identification of preproliferative lesions has placed the

diabetologist under an obligation to detect them early in the hope that photocoagulation will prevent progression. On the debit side the diabetic remains a below average risk for life insurance. The treatment of maturity onset diabetes is in a state of confusion. The debate about the dangers of oral hypoglycaemic agents is still unresolved, while the alternative, dietary treatment, is a failure for the majority of patients. Perhaps the only positive result of the U.G.D.P. controversy has been to focus attention on our ignorance of the causes and prevention of diabetic heart disease in all age groups.

One question which medical students invariably ask at the end of a lecture is 'Is diabetic control worthwhile?'. In the pregnant woman and growing child we know that it is. Furthermore, animal experiments strongly suggest that physiological control of blood glucose levels will prevent or even reverse microangiopathy. There is a growing belief, shared by most of the contributors to this issue, that the same is true in man. However, twenty-four hour blood glucose monitoring has shown just how narrow is the range of physiological normoglycaemia and how infrequently it is achieved by conventional therapy even in 'well controlled' diabetics. The success of the artificial pancreas is impressive but, without greater sophistication in glucose sensors and miniaturization, may represent a false dawn for the majority of diabetics. In the short term, we need to make better use of the resources available to us by motivating and educating our patients to achieve the best possible diabetic control.

I am grateful to the contributors for their efforts in getting this issue out on time and for submitting gracefully to my editorial amendments. I also owe a great debt to my hospital colleagues for shouldering some of my clinical load, to Mrs Valerie Worth for painstakingly checking the references, and to my secretary Mrs Jane Richards for cheerfully typing and retyping many manuscripts. It has been a pleasure to work with Mr David Inglis and his colleagues at W. B. Saunders.

ROBERT TATTERSALL

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Genetics of Diabetes

D. A. PYKE

Diabetes has been called the graveyard of the geneticist's reputation; that may be why geneticists have not contributed much to our knowledge of the subject — they are all dead!

The point is a serious one; people have thought for centuries that diabetes ran in families and that there must be some genetic element in its causation, but they have been quite unable to define it. The most popular view is still that diabetes is a genetic disease, i.e., with rare exceptions, diabetes occurs in those who are genetically susceptible and not in those who are not.

The study of the genetics of diabetes seemed to have lost its way and come to a halt a few years ago, but recently some exciting new observations have transformed the scene and the subject is on the move again. Modern work has thrown light not only on what is genetic in the cause of diabetes but, more interesting and more hopeful, what is not. If diabetes is a genetic disease, in the strict sense described above, it is incurable and unpreventable. But if there are other factors in its production then perhaps we can prevent, delay or ameliorate it.

The purpose of this chapter is to show that there is now good reason to think that diabetes is not exclusively a genetic disease and to point to hopeful signs that may lead to a better understanding of its cause and perhaps to clinical advance.

CLASSICAL STUDIES

I shall not review all the older work on the genetics of diabetes because it has not on the whole been fruitful, and good surveys can be found elsewhere (see Creutzfeldt, Köbberling and Neel, 1976). The most important reason for this is that diabetes is so indefinite a disease. There is no single biochemical cause of the disorder and, therefore, it can be described only in terms of impairment of carbohydrate tolerance, which shows a gradation in normal populations with no clear division between normal and abnormal. Carbohydrate tolerance may also vary in the same individual on different occasions and declines with age so that after the age of 70 the normal glucose tolerance may be abnormal! (Butterfield, 1962).

The diagnosis of diabetes may be easy in the acute-onset case but this type is in a minority and the commoner maturity-onset type shades off into normality.

There are several objections to believing that diabetes is entirely a genetic disorder. First, it is so common. Most disorders depending upon a single gene, such as phenylketonuria or haemophilia, are rare, occurring in perhaps 1 in 10 000 of the general population. Diabetes is about 100 times as frequent. Genetic disorders such as haemophilia are biologically disadvantageous, their victims have shorter than normal lives and the disease would die out if it were not for mutation. But mutations are uncommon, thus these diseases are uncommon — unless there is some clear biological advantage to having the disease. Sickle cell anaemia is the best example of a disease that confers an advantage, but only in malarious countries. Sicklers are less vulnerable to malaria and thus they thrive in those areas, but elsewhere the disadvantage that haemoglobin-S kills is not balanced by any advantage and the disease is consequently rare.

Like sickle cell disease but less dramatically, diabetes also kills; but we know of no advantage of being diabetic and therefore no reason why its prevalence should remain so high. To resolve this paradox Neel ingeniously suggested that in times of famine, such as have occurred throughout human history, it is an advantage to be diabetic (Neel, 1962). The diabetic might be better able to conserve himself in hard times than the non-diabetic.

Unfortunately this theory depends upon there being an excess of insulin in the blood of diabetics — as was at one time thought to be the case, the theory being that diabetes was due to insulin antagonism not deficiency. We now know that diabetes, at least in the majority of cases, is due to insulin lack, complete or partial. The previous contrary view was the result of not appreciating the effect of obesity which leads to insulin resistance and thus to high blood levels of insulin. In the light of present knowledge, therefore, the 'thrifty genotype' theory is out of favour, although Neel thinks it might come again! (Neel, 1976).

We are left with the problem that if diabetes is a genetic disorder why is it so common?

We must accept that there is a genetic component in the aetiology of diabetes, at least in some cases. Family aggregation, occasional striking family histories and twin studies all support this view, and recent studies of histocompatibility antigens confirm it (see Creutzfeldt, Köbberling and Neel, 1976). Discussion has concerned the extent and pattern of inheritance. As I hope to show, the debate has been inconclusive because it has treated diabetes as a single entity; with this approach I do not believe that an answer can be found. The debate so far has mainly concerned two theories — recessive gene or multifactorial inheritance. According to the first theory diabetes is determined by a single, non-sex-linked gene which must be inherited from both parents to produce the clinical disease; according to the second, diabetes results from an interaction between several different genes and environmental factors. One modification of the recessive gene hypothesis was that juvenile onset diabetes appeared in the homozygote and maturity onset diabetes in the heterozygote. On this theory both parents of juvenile onset diabetics should be maturity onset diabetics; they are not and the theory is no longer tenable.

Supporters of single-gene theories have often invoked incomplete

penetrance to explain results which do not come up to expectation. This may be a useful let-out but it devalues the theories since they can no longer be refuted as there is a ready explanation for any inconsistency.

The theory which held the field from 1933 until a few years ago, and still has its adherents, namely that diabetes was due to a recessive gene, was largely founded on the work of Pincus and White (1933, 1934a, b). However, much of its force came from finding the right number of diabetics among the offspring of parents of whom neither, one or both were diabetic. The diagnosis of diabetes depended upon glucose tolerance tests (GTT). If the criteria of abnormality of the GTT were changed, so would be the ratios.

CONJUGAL DIABETES

A crucial observation in the study of the genetics of diabetes is the frequency of the disease among the offspring of diabetic couples. If both husband and wife are diabetic and the disease is due to a single recessive gene then all their children should be diabetic. This line of enquiry should therefore decide whether the recessive theory is correct.

There are difficulties, however. Diabetic couples are not very common; their offspring are sometimes young and therefore, although possibly destined to develop diabetes, may not yet have done so; the offspring may no longer be living with their parents and information about their state of health may therefore have to be obtained indirectly and perhaps inaccurately. However, in spite of these reservations some conclusions can be drawn from the several published studies of conjugal diabetics (see Tattersall in Creutzfeldt, Köbberling and Neel, 1976). They all show a prevalence of overt diabetes among the offspring not of 100 per cent but of about 5 per cent. This figure may rise in time as the offspring of the diabetic parents reach the age of high risk, but in the British Diabetic Association Study (Cooke et al, 1965) 40 per cent of the 'children' of the diabetic couples were aged over 40, so that if all were going to develop diabetes one would have expected to find a considerable number already affected. In that study it seemed that the children of conjugal diabetic parents, one of whom had developed diabetes in early life, had a greater chance than others of becoming diabetic. Whether this is true might be determined by studying children of parents *both* of whom developed diabetes in early life. However, these couples are so rare that no such series has ever been collected.

If we assume that the distribution of the age of onset of diabetes in the offspring of diabetic couples is the same as in the general diabetic population we can calculate the expected final figure for the prevalence of diabetes among the offspring of diabetic parents. On this basis we estimate that not more than 25 per cent of the offspring of diabetic couples might be expected to become overtly diabetic.

A serious weakness in these studies is that they depend upon indirect evidence of the frequency of diabetes in the offspring — information from the parents or answers to questionnaires. This may not matter when considering juvenile-onset diabetes when the diagnosis is usually clear-cut, but in maturity-onset diabetes, where there may be no symptoms or the diagnosis

may be missed, the error of indirect ascertainment may be large. Studies of glucose tolerance on the offspring of conjugal diabetics show a higher frequency of diabetes, perhaps 25 per cent or more, and projections of expected prevalence at age 60 suggest a figure of about 60 per cent (Tattersall and Fajans, 1975b); but in nearly all these cases the parents have the maturity-onset type of diabetes and their children the same. Thus this type of study tells us nothing of the inheritance of juvenile-onset diabetes.

The conclusion from conjugal studies is that they suggest a strong genetic tendency (possibly a single gene) in maturity-onset diabetes but give us no useful information about the juvenile-onset type.

INSULIN ANTAGONISM AND A 'DOMINANT' MODE OF INHERITANCE?

The theory that diabetes is due not to insulin lack but to insulin antagonism, that this antagonism resides in the B chain of insulin and on electrophoresis is associated with the albumin fraction and that this 'synalbumin' insulin antagonist is inherited as a Mendelian dominant (Vallance Owen, 1966) has confused and baffled many observers. The basis for this theory is unsure — all sera on testing by the method used for measuring 'synalbumin' antagonist show some insulin antagonism; nevertheless, results have been expressed as 'positive' or 'negative' according to whether they exceed an arbitrary limit. Furthermore, the results have not been widely confirmed (Davidson and Poffenbarger, 1970). The suggestion that the general population consists of two distinct groups, 'synalbumin' positive and negative, is based on fallacious selection of cases (Pyke, 1970).

Observations on 'synalbumin' insulin antagonism have contributed nothing positive to our understanding of the cause or inheritance of diabetes.

TWIN STUDIES

Twin studies as an approach to the understanding of the cause of disease have a long history. They give evidence of the inherited basis of a disease if they show its frequency to be greater in identical (monozygotic) than in non-identical (dizygotic) twins.

Some years ago twin studies fell out of favour. There were two reasons for this.

First, concordance between identical twins, i.e. when both twins have the same disease, was taken to show that the disease was inherited. However, identical twins, especially in early life, share the same environment as well as the same genes so similarity between them might be due to genetic *or* environmental causes. Only if identical twins show a higher degree of concordance than non-identical and if there is no difference between the two types in respect of the number of pairs living together or apart can it be inferred that concordance is due to genetic causes.

Second, some of the earlier twin studies were of psychological features and psychiatric disorders. These are notoriously hard to measure or define and the value of twin studies is therefore correspondingly limited.

Twin studies have tended to concentrate too much on similarities between pairs instead of on differences. Similarity between identical twins may be genetic or environmental in origin, differences must be environmental. Early twin studies of diabetes (reviewed by Langenbeck and Jörgensen, 1976) showed that concordance was higher in identical than in non-identical twins and thus that genetic factors were important. Then Berg, in a paper which is much quoted (because her findings were described in a 'letter from Germany' in the *Journal of the American Medical Association*) but, I suspect, little read (because published in 1938 in a German journal of racial biology), showed that all identical twins over the age of 43 were concordant, i.e. both were diabetic (Then Berg, 1938, 1939). The significance of this observation seems to have been lost until recently but it is confirmed by two more recent studies Harvald and Hauge (1963), working with the Danish twin registry, found a high degree of concordance and assumed that all twin pairs would eventually become concordant. They made this assumption, however, because most of their pairs were maturity-onset diabetics.

The Joslin clinic study showed similar results (Gottlieb and Root, 1968). All 10 maturity-onset pairs, but only 5 of the 20 juvenile-onset pairs, were concordant.

The lesson is clear from these three twin studies; maturity-onset identical twin pairs are almost always concordant, juvenile-onset pairs often discordant. The significance of this finding is increased by the fact that most older-onset pairs are living apart at the time of diagnosis of diabetes whereas many juvenile-onset twins are still living together.

There is an important reservation to make about drawing conclusions from concordant:discordant ratios. There is a bias in favour of the ascertainment of concordant as against discordant twin pairs — the concordant pairs with two diabetics have twice as much chance of recognition. In our own collection of twins we have found differences in concordant:discordant ratios according to the source of ascertainment of the twins. Of those discovered through press, radio and television nearly all were concordant and among our own clinic patients 19 pairs were concordant and 7 discordant, but of those notified to us by other physicians nearly half the pairs were discordant. The reason for these differences may be that among those listening to radio and T.V. programmes it is assumed that we are interested only in concordant pairs, or perhaps older pairs no longer think of themselves (or their doctors no longer think of them) as identical twins. On the other hand, our colleagues who notify cases to us may know of our particular interest in unaffected twins, i.e. in discordant pairs, and therefore make a special point of telling us about these pairs. Whatever the reasons for the differences, overall concordant:discordant ratios should not be regarded as giving a true figure unless it is certain that *all* twin pairs in a defined population have been discovered.

King's College Hospital Twin Series

We have at King's College Hospital collected 125 pairs of identical twins one or both of whom have diabetes. This is now the largest series of diabetic

identical twins and, as they have been personally observed and followed for up to 10 years, they provide a valuable source of information.

Method of collection

The twins have been collected from four main sources — our own clinic, from colleagues who, knowing of our interest, have told us about their own cases and generously allowed us to study them, through press, radio and television and through the British Diabetic Association. The numbers of twin pairs in each of the four groups are approximately equal but the proportions of concordant to discordant are not.

It is, of course, essential to be sure that the twins are monozygotic or 'identical'. In practice, there is no difficulty; the story of being indistinguishable, even to their parents, and, in the case of younger pairs, their striking similarity of appearance leave little reason for doubt, 'the one so like the other as could not be distinguish'd but by names' (Shakespeare: *The Comedy of Errors*). However, to provide scientific support for a simple clinical observation, 12 group blood grouping has been carried out on all available twin pairs; by this method the error in establishing zygosity is less than three per cent. The serological method has, in practice, never refuted the clinical diagnosis.

Although we have a relatively large series of twins we can deduce, by mapping their distribution in the country and calculating the number of diabetic identical twins one would expect to find in a population of 50 million, that we have studied only a small fraction of all diabetic identical twins in Britain.

Whole series

The whole series now consists of 125 pairs, 85 concordant, 40 discordant. I have already explained that the overall concordant:discordant ratio may mean little but there is a striking difference in the ratio if the series is divided by age at diagnosis. Under the age of 45 there are roughly equal numbers of concordant and discordant pairs, but over this age all pairs are concordant. This remarkable finding surprised us, but it should not have done. In the previously published series there has been a strikingly high concordance rate in older twins, indeed Then Berg (1938) spoke of 'absolute heredity' after the age of 43, but the significance of the finding was not appreciated. In our own series we have still not seen a pair in whom one twin was diagnosed over the age of 45 in whom the other twin was not also known, or found to be, diabetic. Presumably such pairs exist; Gottlieb and Root (1968) have reported two possible cases, but we have not yet seen any.

It might be argued that the reason why the younger-onset twins are often discordant is that the second twin will develop diabetes but has not yet had time to do so. We do not think this is the explanation for discordance for two reasons. First, most concordant pairs develop diabetes — or, more exactly, are discovered to be diabetic — within a few years of each other. Of 50 concordant pairs aged under 45 at diagnosis the twins developed diabetes within three years of each other in two-thirds and within 10 years in 90 per cent. On the other hand over half of the discordant twins have been

discordant for more than 10 years. The criticism that we have not made adequate allowance for the declining reservoir of discordant pairs as some pairs become concordant with the passage of time (Rosenthal, Goldfine and Siperstein, 1976) does not, in our opinion, invalidate this approach (Pyke, Theophanides, and Tattersall, 1976). The *rate* of becoming concordant after a few years declines from about nine per cent a year at onset to three per cent at 11 to 20 years. Furthermore of the 10 pairs who were still discordant after 20 years and who have been observed for an average of another six years only one has subsequently become concordant. Three of the remaining pairs are still discordant after 32, 34 and 36 years.

Second, the unaffected twins of the discordant pairs show no sign of becoming diabetic. We have done repeated glucose tolerance tests on the unaffected twins — 20 pairs have been tested for more than six years — and none has shown any deterioration; mean blood glucose values during glucose tolerance tests are actually slightly lower and mean insulin values slightly higher in the latest test than in the first. Nor has a single unaffected twin developed clinical diabetes during the years that we have been observing them, to our disappointment, because we would like to be able to re-test stored sera taken *before* a twin became diabetic when we know that he has later become so, and to our surprise, because we have tested nine of these discordant pairs from the time of diagnosis of diabetes in the affected twin and we might have expected two or three of them to develop diabetes in three years. It seems therefore that some of the early-onset twin pairs will remain discordant, perhaps indefinitely, and that the unaffected identical twin is not always destined to develop diabetes.

In making our division at age 45 at diagnosis we are to a large extent separating insulin-dependent from non-insulin dependent diabetics. Thirty-nine of 45 younger pairs were on insulin, 23 of 32 older-onset pairs were not (in one younger and two older pairs the twins were on different treatment; but in all the rest treatment was the same in both twins).

If identical twin pairs can be discordant for diabetes it follows that, in these pairs at least, diabetes cannot be wholly genetic in origin. This illustrates one of the important values of twin studies, namely the greater significance of differences than of similarities between twins.

NON-GENETIC CAUSES

The realization that juvenile-onset diabetes may be, in part at least, of non-genetic origin has increased interest in the search for non-genetic or environmental causes. There are broadly three possible theories of the role of genetic and environmental factors in the origin of juvenile-onset diabetes (Table 1).

Theory 1. Diabetes in the concordant pairs is due to genetic factors, and in the discordant pairs entirely to non-genetic, environmental factors.
Theory 2. This is the reverse of theory 1. The genetic predisposition is the same in both concordant and discordant pairs but both members of the concordant pairs and the affected members of the discordant pairs have met