Section of Experimental Medicine and Therapeutics

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DISCUSSION ON THE CAUSE OF DIABETES

Professor F. G. Young: *Experimental Observations on the Cause of Diabetes.*

Since more than one clinical condition may be included under the term diabetes mellitus, and since there are a number of different methods of inducing a diabetic condition experimentally, it is probable that there is more than one fundamental problem to be considered under this heading. Experimentally there are five main methods of inducing diabetes, three of which involve direct or indirect interference with the pancreas:

(*a*) Complete or partial pancreatectomy.

(*b*) Administration of alloxan, which leads to a rapid necrosis of the β cells of the pancreatic islets.

(*c*) The administration of anterior pituitary extracts, which may lead to a persisting diabetes associated with lesions of the islets of Langerhans.

(*d*) The administration of excessive glucose, which may also lead to the development of islet lesions.

(*e*) The administration of certain adrenal-cortical steroids.

Recently Dohan and Lukens [4] have described the induction of glycosuria in partially depancreatized and in normal cats by the intraperitoneal injection of 20% glucose twice daily for some weeks. In two partially depancreatized and in one normal cat the glycosuria persisted after glucose treatment ceased. Lesions of the pancreatic islets were found in such animals and were presumably the result of overwork exhaustion. These observations emphasize forcefully the classic view that a high blood-sugar level can be harmful to the islets of Langerhans.

In 1941 Ingle [9] showed that the administration of large doses of certain adrenal-cortical steroids to normal rats forced-fed a high carbohydrate diet at a normal caloric intake could induce glycosuria; this condition was relatively insensitive to control by insulin [11]. The effective steroids all carried an oxygen atom at position 11 in the nucleus, and probably stimulated gluconeogenesis in the liver [12]. It was a natural corollary to find that large doses of pituitary adrenocorticotrophin will induce glycosuria in normal forced-fed rats [10].

There is good evidence that the anterior pituitary gland can influence carbohydrate metabolism by two separate pathways only one of which is mediated by the adrenal cortex. Clinically both acromegaly and pituitary basophilism may be associated with glycosuria, the first of these conditions being related to overactivity of the *a* cells of the anterior pituitary lobe, while the second is associated with activity of the adrenal cortex as well as with changes in the β cells of the pituitary gland. The action of the so-called diabetogenic factor of anterior pituitary extracts is not mediated by the adrenal glands [6, 7, *see also* 5] and we find the agent responsible for this effect to be closely associated with, if not identical with, the pituitary growth hormone [3, 16, 20, 21]; an observation obviously relevant to the frequency of diabetes in acromegaly.

It is convenient to distinguish two types of diabetes experimentally induced in normal animals (adult dog or cat) by treatment with diabetogenic anterior pituitary extract: (1) idiohypophyseal diabetes, which is the diabetic condition which exists during a period of treatment with diabetogenic extract, and which may disappear on cessation of the treatment; (2) metahypophyseal diabetes, the condition which may persist after cessation of pituitary treatment. The induction of idiohypophyseal diabetes is accompanied by nitrogen retention and an increase in body-weight [20] and in the dog the condition is somewhat less sensitive to control by insulin than is pancreatic diabetes, in the early stages at least. If, however, treatment with the diabetogenic pituitary extract is prolonged until the condition of idiohypophyseal diabetes begins to pass into that of metahypophyseal diabetes, gross insensitivity to the hypoglycæmic action of insulin may develop. In the dog the ease of development of idiohypophyseal diabetes is apparently related to the amount of protein

(meat) in the diet (fig. 1), the dog receiving a high-carbohydrate or a high-fat diet being less sensitive to the diabetogenic action of administered anterior pituitary extract than a dog fed on meat. Whether such observations are relevant to other species, and to man in particular, is not known at present.

Metahypophyseal diabetes has been induced in the dog and in the cat [21]. In the dog it usually increases in intensity with time, although, unlike the depancreatized dog, the dog

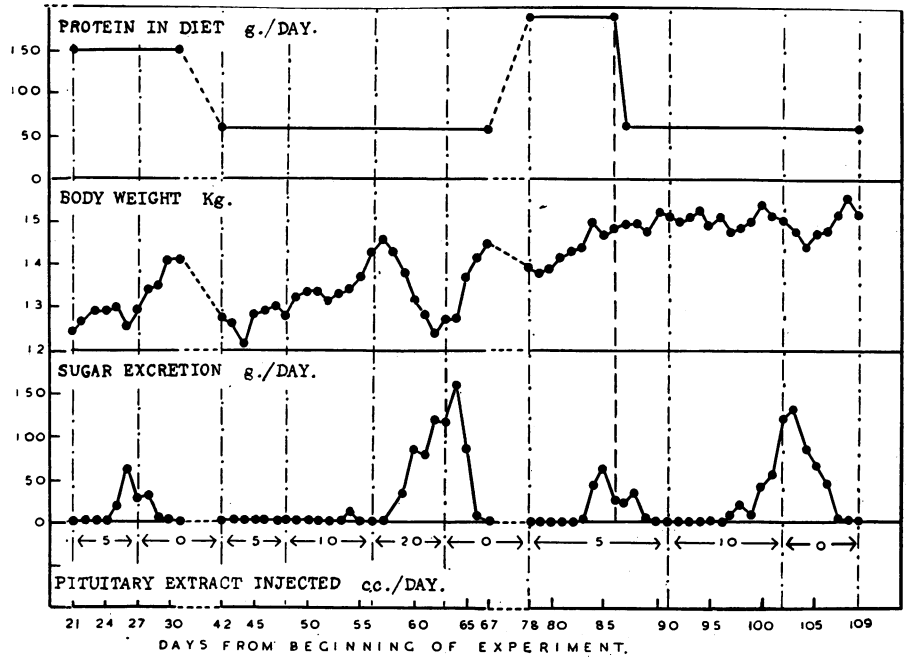

FIG. 1.—The influence of the composition of the diet on the susceptibility of the normal dog to the experimental induction of idiohypophyseal diabetes. The diet consisted of horse meat and liver with or without the admixture of biscuit. The daily calorie intake was approximately constant throughout the whole experimental period.

with metahypophyseal diabetes may survive for a long time without insulin treatment and with little or no ketonuria. The condition is associated with lesions of the islets of Langerhans of the pancreas, which may range from mild degranulation of the β cells to almost complete hyalinization of the islets [17]. In the cat an initially severe metahypophyseal diabetes may undergo remission and disappear either spontaneously or as the result of treatment with insulin [21]. In such cured animals complete hydropic degeneration of the β cells of the pancreatic islets has been observed [18, 21] and the reason for the disappearance of the diabetic condition remains unexplained [*cf. also* 4].

In the dog with metahypophyseal diabetes the ketonuria, which tends to increase with time, is enhanced by the feeding of a meat diet, and is substantially diminished if the diet contains a high proportion of fat (beef suet) [13, 19]. These observations with dogs are in good agreement with the finding of Petrén, F. M. Allen, Newburgh and others who, in the days before insulin was generally available, successfully treated clinical diabetic ketosis with high-fat diets [*see particularly* 14]. These results are not in agreement with the present theoretical views of the mechanism of ketogenesis and they are often neglected.

The recent work of Dr. and Mrs. Cori and their collaborators [1, 2] has shown that certain anterior pituitary extracts can depress the activity of the enzyme hexokinase *in vitro*, and that this depression can be counteracted by the *in vitro* addition of insulin to the system. Since the enzyme hexokinase catalyses the conversion of glucose to glucose-6-phosphoric acid at the expense of a phosphoric acid grouping from adenosine triphosphoric acid, and since the formation of glucose-6-phosphoric acid may be an essential preliminary step in the utilization of glucose for many, perhaps all, metabolic processes in the body, the importance of the observed antagonism between anterior pituitary extracts and insulin with respect to hexokinase activity becomes apparent. Unfortunately it has not been possible to establish a simple identity between the pituitary diabetogenic substance and the pituitary factor which inhibits hexokinase activity *in vitro* [15] and since insulin is excessively effective

in hypophysectomized animals [8] it is possible that insulin exerts some action in addition to that of releasing hexokinase from the depressive action of pituitary factors, in bringing about its characteristic physiological action. It is clear that further investigation of the influence of hormones on enzyme systems *in vitro* may yield additional results of the greatest physiological significance.

It is encouraging to find that recent research leads to the belief that many apparently diverse means of inducing experimental diabetes all exert a common action on the islets of Langerhans of the pancreas, and also that insulin deficiency and a physiological excess of an anterior pituitary factor may both act upon the same enzyme system. Thus it is possible that all diabetogenic agents may have relatively few points of attack upon the normal processes of carbohydrate metabolism, of which the enzyme hexokinase may be of outstanding importance.

Since we may now conceive of such possible simplifications in accepted theories of the ætiology of experimental diabetes it is not unreasonable to hope that the clinical picture may also prove to be susceptible to such clarifying procedures in the not far distant future.

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Mr. K. C. Richardson (Reader in Histology, University College, London) demonstrated to the Meeting, by means of slides, the lesions and proliferations mentioned by Professor Young in his communication.

Dr. R. D. Lawrence: *Alloxan Diabetes*[1] [*Summary*].

The injection of alloxan produces diabetes in a wide variety of species. This it does by an immediate specific toxic action on the β cells which is not chemically understood, but leads to permanent *atrophy* of the *islets* with permanent diabetes. It has been administered therapeutically to human cases of endogenous hyperinsulinism from pancreatic insulinomata without any obvious effect on the cells of these tumours. But such a case is reported by Conn *et al.* (1947, *J. Lab. clin. Med.*, **32**, 347) in which permanent diabetes developed after the removal of the tumour, indicating damage to the remaining normal islet tissue from alloxan. There is no evidence, so far, that alloxan is connected with naturally occurring human diabetes but it is a potent and interesting experimental tool for animal experimentation.

Alloxan points the way to the interesting possibility that other chemical agents may be found with a specific toxic action on other cells producing specific hormones or catalysts, such as the pituitary, adrenal, &c. From this aspect the discovery of alloxan diabetes is stimulating and should be borne in mind by research workers.

Professor H. P. Himsworth: *Diet in the Ætiology of Human Diabetes.*

During wars the diabetic death-rate tends to fall. Closer analysis reveals that this is related, not to actual war, but to food shortage, for no such decrease occurs in belligerent countries whose food supplies are unaffected while it falls significantly in neutrals subject to privation [1]. This association is evident in the comparative mortality indices for England

[1]For detailed work refer to LUKENS, F. D. W. (1948) *Physiol. Rev.*, **28**, 304.

and Wales (fig. 1) which show that the falls are co-terminous with food restriction rather than hostilities.

In World War II food restrictions began in 1940 and have not yet been ameliorated. If such restrictions affect mortality a time lag of at least a year would be expected before their

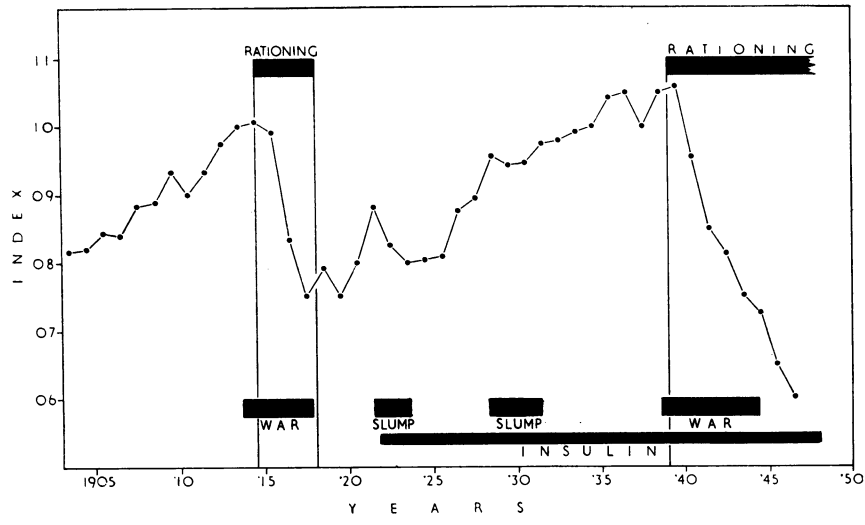

FIG. 1.—England and Wales. Diabetic mortality: comparative mortality indices (1938 basis). Showing the effect of food restrictions on diabetic mortality. (The figures for 1946 and 1947 have kindly been supplied by Dr. Percy Stocks.)

effects became manifest. Fig. 2 shows the changes in the daily, *per capita*, consumption of different foods from the diet of 1939 to the diet of today [2]. Below is given the change in female diabetic mortality; the female rate being chosen as less influenced by mobilization, the curve being antedated one year to allow for the time lag. The protein curve bears no relation to the mortality curve; a possible correlation—direct in one, inverse in the other—may exist for the calorie or carbohydrate curves; but the correlation between the mortality and fat consumption curves is striking.

There is a mass of evidence with similar import [1]. The progressive rise in diabetic mortality in Western countries during the last fifty years coincides with a gradual change towards higher fat and lower carbohydrate diets, the protein and calorie values have altered little. The diabetic mortality rate is high in countries whose diets tend to be high in fat and poor in carbohydrate; and low where the opposite tendency prevails. The fall in diabetic mortality in World War I was related to a fall in fat and rise in carbohydrate intake. The higher urban, as compared with the rural, diabetic mortality is associated with a higher fat and lower carbohydrate consumption in towns. Diabetic mortality rises with economic position and, simultaneously, dietary habits change so that a greater proportion of fat and less carbohydrate is taken. Race is not a predominant factor in determining diabetic mortality. Immigrant races manifest the mortality rate of their new country in proportion as they acquire its dietary habits.

There thus seems to be a universal relation between diet and diabetic mortality. The dietetic factor most closely related is fat consumption. But that is not to say that fat *is* the deleterious factor; it may simply serve as an indicator of other, and more important, contingent variables such as calories.

If, as seems indisputable, the conspicuous and continued fall in the diabetic mortality of this country, which occurred on both occasions when food rationing was necessary, is no artefact then it must be due to one of three factors, or a combination of them; a change in certification of deaths in known diabetics, a lower fatality rate among existing cases of diabetes, or a falling incidence of the disease.

The following facts seem to exclude failure to record diabetes on the death certificate as the explanation. The fall in mortality is confined to the older age-groups (fig. 3); after World War I the fall was replaced by a rise while, after World War II, it continued although the civilian medical profession returned to full strength; there is no reason why on two separate occasions failure to certify should coincide with rationing.

Equally improbable is a marked decrease in fatalities among existing cases of diabetes. No indication of this was observed by the medical profession. No notable improvement

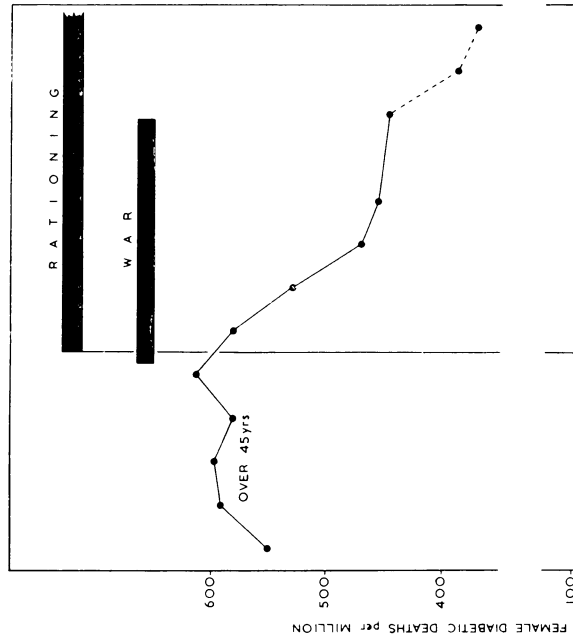

FIG. 3.—Female diabetic mortality and age (1935–47). Showing that the fall in diabetic mortality is entirely due to a fall in mortality in the older age-groups. The figures for 1946 and 1947 are provisional. The figures after 1939 have been recalculated to the pre-1940 basis of presentation in accordance with the Registrar-General's Report of 1940.

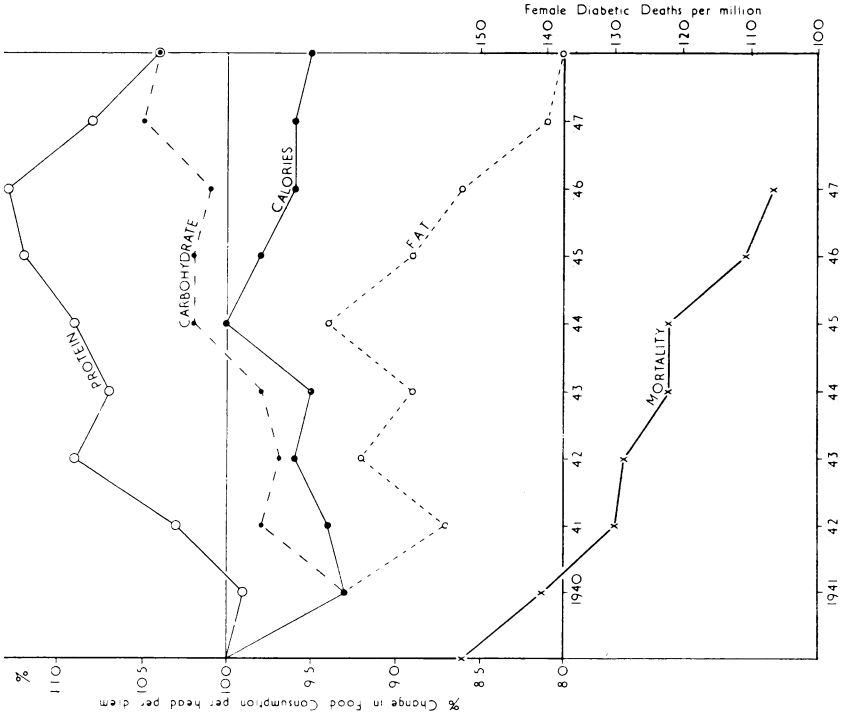

FIG. 2.—England and Wales. Food consumption and female diabetic deaths. Showing the correlation between food consumption [2] and diabetic mortality rate. The female rate is chosen as less influenced by mobilization, and the curve is antedated one year to allow for time lag.

in therapy occurred. The introduction of insulin produced no such fall. Neither can inadvertent enforcement of dietetic therapy by rationing be invoked for, in World War II, special diets, differing little if at all from the pre-war standard, were available and, in World War I, rationing was mild when compared with the therapeutic restrictions imposed on diabetics before that war when the mortality was rising. Finally the death-rate among young diabetics, from being steady, actually rose after 1939 [3].

There remains a decreasing incidence of diabetes as the explanation. Available evidence indicates that diabetic mortality rates reflect incidence rates. Statistics of the number of applications for diabetic rations have been collected by the Ministry of Food for the Food Rationing (Special Diets) Advisory Committee of the Medical Research Council. Owing to the stringency of rationing and the liberal benefits available to diabetics, these are unlikely to be an underestimate of incidence. In England and Wales in 1945 the total number of deaths from diabetes among males was 1,364, among females 2,662. In the same year 35,500 males and 54,297 females (with 2,100 persons of unstated sex) were obtaining diabetic rations. By 1945 applications had stabilized at 2,350/M., and in 1947 were 2,310/M. In the same years the mortality rates were 106/M. and 84/M. respectively. In 1935 a large sickness survey in U.S.A. revealed a diabetic incidence rate of 3,673/M. [4], i.e. 50% more than in this country in 1945. The diabetic mortality rate for U.S.A. as a whole at that time was 222/M. There thus seem good reasons for believing that conspicuous and consistent differences in diabetic mortality rates broadly reflect changes in incidence rates.

In 1938 Newburgh and his colleagues [5] drew attention to a common type of middle-aged diabetic who, when made to lose weight, lost all symptoms of diabetes, glycosuria and hyperglycæmia. Fig. 3 shows that the fall in diabetic mortality, and therefore the presumed fall in incidence, since 1939, has occurred entirely among the middle-aged and elderly. Common experience shows that since rationing the majority of people in the country have lost weight. It is suggested that many elderly people, who on pre-war diets would have developed diabetes, are now not doing so, and that it is to the reduced incidence of such cases that the fall in mortality is mainly due. That is not to imply that on cessation of rationing the "mortality rate debt" will have to be paid off. Such cases are probably dying now of cardiovascular diseases, but without developing diabetes.

The general explanation suggested for the data available in 1935 was to the following effect [1]: Susceptibility and hereditary predisposition undoubtedly play a part in the ætiology of diabetes but it is difficult to explain the great variations in diabetic mortality, during the last thirty years, by widespread alterations in the distribution of hereditary susceptibility. A more reasonable explanation is that susceptibility is widespread and that the increasing pressure of some environmental factor is disclosing its prevalence. It seems possible that diet is this external factor. Any population will contain an unknown number of individuals of varying susceptibility. When the diet of their country is rich in carbohydrate and poor in fat it will provoke diabetes only in the most susceptible. But if the diet changes progressively towards a higher caloric, higher fat and lower carbohydrate diet it will provoke diabetes in less and less susceptible individuals and the incidence of diabetes in a population will continue to reflect the dietary habits. The new data presented in this paper strengthen these conclusions.

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Dr. H. Harris: *Heredity in Diabetes Mellitus.*

It is now generally accepted that heredity is an important factor in the ætiology of diabetes, but although various hypotheses have been put forward, the exact mode of inheritance is still very far from clear. Some writers, e.g. Levit and Pesikova (1934) have postulated a single semi-dominant gene as a determining factor in all cases, others, e.g. Pincus and White (1933), Hanhart (1947), have suggested that a single recessive gene was responsible, and others, e.g. Cammidge (1928), Wright (1931), have thought that the disease might on some occasions be determined by recessive and in others by dominant genes. A study of the literature suggests that it is unlikely that any very simple formula can adequately account for all the observed phenomena.

Diabetes is a disease which has a very wide range of expression. It may be very severe or quite mild, and it may come on at any time in life from childhood to old age.

Fig. 1 shows the distribution of a series of over 2,000 patients according to the age at onset of the disease. These patients represent a random sample of all the patients who have attended at King's College Hospital Diabetic Clinic between 1930 and 1947. The distribution has a very characteristic appearance, the main hump occurring between about 45 years and 70 years. It will be seen that until about the age of 40 there are approximately equal numbers of the two sexes affected, while between 40 and 70 there are considerably more female than male patients. The relative preponderance of the late onset type of case occurs in both sexes, and it is probably even more marked in the general population than would appear from fig. 1, because it is likely that this distribution underestimates considerably the

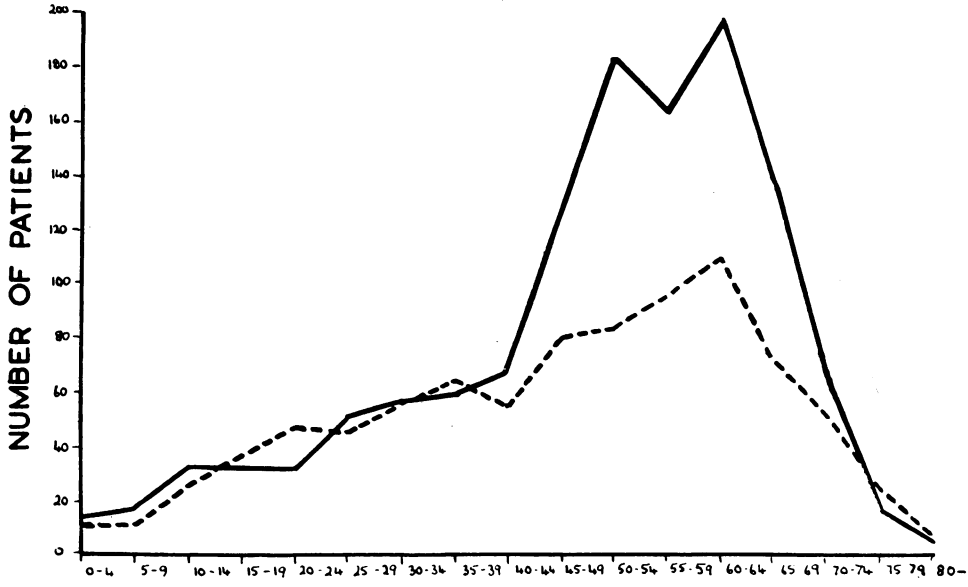

FIG. 1.—Age at onset of 2,132 diabetics attending King's College Hospital, 1930–1947. Males = interrupted line - - - - - - - - - - - -. Females = continuous line ——————.

relative frequency of the older diabetics and exaggerates the relative frequency of the younger ones. This is so because the latter are generally severe cases and all find their way to a hospital clinic while the former are on the whole milder and many probably are not sent to hospital at any time.

A question of some interest to the geneticist is the following: Are hereditary factors of any importance in determining the time of life when the disease develops or the degree of its severity? In other words is diabetes genetically homogeneous or heterogeneous? If it is genetically homogeneous we must assume that all the variation in the severity and age of onset of the condition is determined by environmental factors. If it is genetically heterogeneous then it would be likely that at least some, and perhaps a great deal of the variation in its expression could be accounted for by hereditary differences. A special instance of the latter situation would occur if, in fact, diabetes is not a single disease entity but really several genetically distinct diseases.

There is evidence which suggests that hereditary differences do play an important part in determining the form and character that the disease may assume.

If we take a series of diabetic patients we find that on the average about 5% of their brothers and sisters have also developed the disease. Now if hereditary factors determine, not merely which individuals develop diabetes, but also the type of the disease that develops, we might expect to find that, if two brothers or sisters are diabetic, then they would tend on the average to resemble one another in the form of the disease, more than any two diabetics taken at random. Thus we might expect that the brothers and sisters of juvenile diabetics would be more likely to develop the disease in early life than would the brothers and sisters of middle-aged or elderly diabetics.

To examine this point a series of 1,241 diabetics have been investigated, and it was found that they had, in all, 3,827 brothers and sisters of whom 166 were also diabetic. Fig. 2 is a diagram showing 158 of these diabetic sibs arranged according to the age at onset of the disease. The outstanding feature of this diagram is the way in which, as the age at onset of the original case (the propositus) rises, so the average age at onset of the disease in the diabetic

brothers and sisters also goes up. One difficulty, however, in the interpretation arises from the fact that, in general, the propositi in the younger age-at-onset groups do not have many sibs who are very old and so we do not know if those still unaffected may not develop the disease later in life. If this were to happen then it would tend to fill up the top right-hand corner of the diagram and the regression would be less marked. However, it is clear that most of the sibs of the older cases could have developed the disease in early life while, in fact, very few of them did. In other words the diagram suggests that the juvenile and young adult form of the disease is much more likely to develop among the sibs of the juvenile and young adult diabetics than among the sibs of the middle-aged or elderly diabetics. A more rigorous statistical analysis of the data has confirmed this conclusion and it seems that a significant positive correlation exists between diabetic sibs with respect to age at onset of the disease. This effect seems to be too great to be accounted for by environmental agencies occurring within different sibships, and is in favour of the idea that the juvenile and young adult type of case are genetically separate from the type of case occurring later in life.

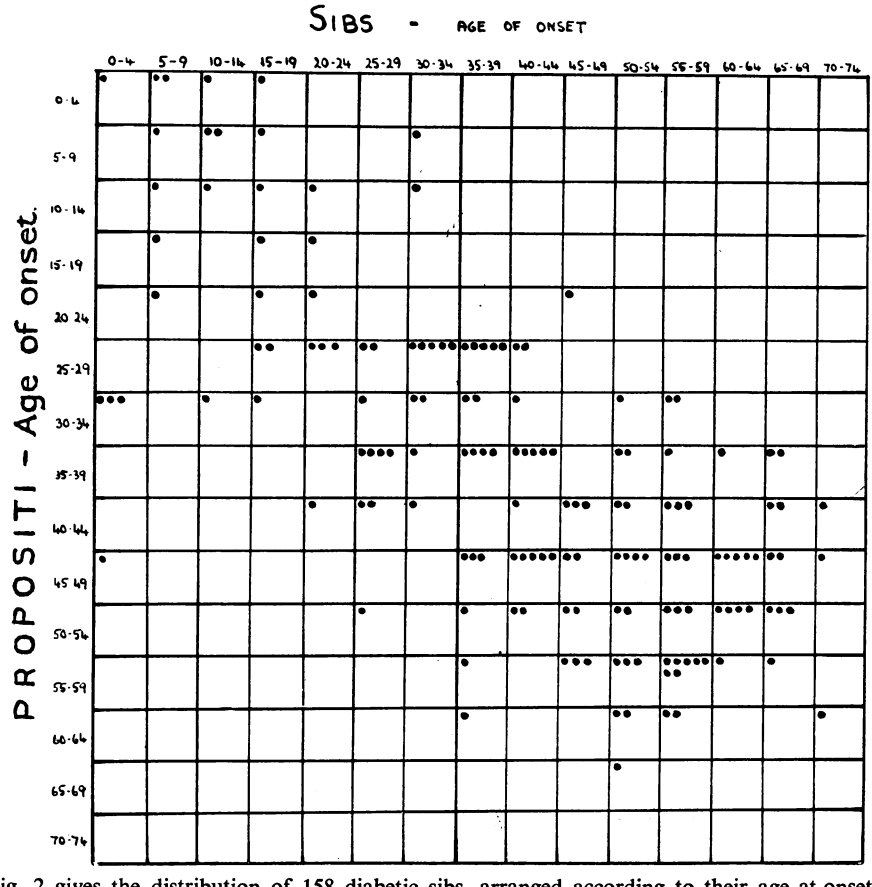

Fig. 2 gives the distribution of 158 diabetic sibs, arranged according to their age at onset and the age at onset of the propositus.

It is well known that when a disease is determined by a recessive gene we may find an increased frequency of cousin marriages among the parents of patients suffering from the disease. The rarer the disease, the higher tends to be the incidence of parental consanguinity. The incidence of cousin marriages in the general population of England is known as a result of the survey of hospital patients made by Dr. Julia Bell (1940). If there is found, in a series of cases of any condition, an incidence of parental consanguinity which is significantly in excess of the level in the general population then that is good evidence that one or more recessive genes are causally important. Furthermore, if in a disease it is found that one type of case differs strikingly in the incidence of parental consanguinity from another type of case, this suggests that the condition is heterogeneous, and the two types of cases are determined by different gene combinations. In the series of 1,241 diabetics it was found that

where the diabetes developed before the age of 30, there was a slight but significant increase of cousin marriages in the parents, whereas this was not observed in the cases developing after the age of 30—the implication being that there are hereditary differences between the juvenile and young adult cases on the one hand and the middle-aged and late onset cases on the other.

While such evidence is, perhaps, in favour of the view that there are two diseases, there is other evidence which suggests that the situation is rather more complex. It is not unusual to find one or other of the parents of a young diabetic is also diabetic, and generally when this is so, the parent suffers from the late onset, milder type of the disease. This, at first sight, is hardly in line with the hypothesis of two genetically distinct disorders, but it might be explained by assuming that the milder late onset type of cases were heterozygotes (i.e. carriers) for the abnormal gene while the more severe, juvenile and young adult type are homozygotes. The milder cases would have a single dose, the severer cases a double dose of the same gene. Such a hypothesis would certainly account for some of the things we know about the familial distribution and the population frequencies, but a great deal more work must be done before we can draw a clear picture of what is going on.

Another aspect of diabetic heredity which will perhaps serve to emphasize the complexity of the whole problem is that which concerns the varying manifestation of the disease in the two sexes in different families. If we take a series of female diabetics we find that they have many more diabetic sisters than brothers. On the other hand among the close relatives of the male diabetics the two sexes tend to be much more equally distributed. This was first observed by Penrose and Watson who noticed both in the data recorded in the literature and in a series of cases of familial diabetics collected by themselves a relative excess of like-sexed pairs of diabetic sibs and a relative deficiency of pairs of unlike sex. The same phenomenon occurs in the brothers and sisters of our series of 1,241 diabetics. Statistically the effect is highly significant. The implication would appear to be that in some families the disease mainly picks out females and in other families mainly males and this occurs to a greater extent than if this were simply a random process. It seems likely that the effect mainly occurs in the families of the milder types of case.

It is known that in the general population there are proportionately more female than male diabetics and there is evidence which suggests that the sex ratio has altered over the last seventy years, and also that it may vary in different social strata and in different populations. Such variations are probably environmental in origin. The observations described above, however, suggest that hereditary factors can also influence the relative frequency of the disease in the two sexes. What the exact interrelationships of the different factors are, however, has still to be analysed.

Another side of the problem of the heredity in diabetes is concerned with the way diabetes is maintained in the general population. Individuals who develop diabetes while young are more liable that non-diabetic members of the population to die before they have passed through and completed the reproductive phase of their lives. Even if they do not die they are less liable than the average member of the community to have living children. In other words their effective fertility is diminished and, on the average, they will contribute less, genetically, to the next generation than individuals not so affected. The later the disease develops, the less likely is it to diminish effective fertility. Thus it would appear that natural selection works particularly against the juvenile and young adult diabetics and one might expect that the particular genes determining this type of the disease should on the average, tend to be less well represented in the population in each succeeding generation. If this were the only factor determining the frequency of the appropriate gene in the population, we might expect that the incidence of the disease would be steadily falling and indeed it would be difficult to see how it had ever reached the quite high incidence that, in fact, exists today.

One counteracting tendency to offset this trend probably is the occurrence of "spontaneous" mutations of "normal" genes to genes predisposing to diabetes. This is almost certainly occurring, but it seems unlikely that the mutation rate is sufficiently high to offset the loss due to selection. Another possibility is the following: There are probably individuals who are not themselves diabetics or who, perhaps, only develop diabetes in late life, yet who, nevertheless, carry one or more of the genes which, in the appropriate combinations, would give rise to the juvenile form of the disease in their offspring. If such individuals had, on the average, slightly more living children than the ordinary member of the population then the gene frequency would perhaps be maintained, and the loss due to selection balanced. Such a hypothesis is at the moment highly speculative, but it is of interest to observe that there is a little evidence which may point in this direction. The Registrar-General (1944) has published figures which suggest that the proportion of women who have had one or more children is higher among elderly diabetics than among non-diabetics of the same age-

group. Of course such figures may well be open to other interpretations. Such a phenomenon, if it occurred, might be analogous to that of heterosis in animal and plant genetics.

This whole problem of how the disease is maintained in the general population has received very little consideration in the past and seems worthy of closer study.

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Dr. W. M. Crofton said that the most ordinary lesion of the cell islands, not the sole one causing dysfunction of the β cells, was a sclerosis beginning as an invasion of the islets by small spherical cells, i.e. fibroblasts. This was caused by the virus phase of non-pyogenic microbes which could, invariably, be isolated from the patient's urine. By autogenous immunization the case could be cured, provided that the destruction of the islet cells had not gone beyond redemption.

It was fortunate that if the infection was overcome, surviving islets could hypertrophy and so produce sufficient islet internal secretion for tissue metabolism.

Quite recently he had enabled a veterinary surgeon to cure completely a dog with typical symptoms of wasting polyuria, polydypsia, polyphagia, and glycosuria. The microbe isolated from the dog's urine was a staphylococcus.

Dr. Mary Walker suggested that much of the recent fall in the mortality of diabetes was due to the use of sulphonamides and, especially, of penicillin. Prior to their use many diabetics died of infective gangrene, carbuncles and pneumonia.

Dr. S. M. Hilton said that Professor Himsworth had shown them a remarkable correlation between the death-rate of sufferers from adult-type diabetes and the composition of the national diet: changes in the former closely followed changes in the latter, with a lag of about a year. He had suggested that these findings supported the hypothesis that certain dietary factors had a rapid effect on the incidence of the disease.

If this were so, and it be assumed that sufferers from adult-type diabetes live on the average for, say, five years, then it would take over five years before the full effect of one change in diet was realized, and if the diet were being changed continuously (as occurred in the data just presented), the death-rate of adult-type diabetics would follow a complicated course and would not show the simple relationship that Professor Himsworth had demonstrated.

Professor Himsworth, in reply, said that Dr. Hilton's criticism was the essential point in favour of the hypothesis he (Professor Himsworth) had put forward. The apparent association between diet and diabetic mortality could not be explained by the effect of diet on the survival of *established* cases of diabetes. It could only be explained by its effect on those *persons who had not yet developed diabetes* but who would have done so if circumstances had permitted their taking an unrestricted dietary, i.e. by its effect on the incidence of new cases of diabetes. Every physician was acquainted with the obese patient with glycosuria who showed an unequivocal diabetic type of blood-sugar tolerance curve, and who, when his weight was reduced, rapidly lost his glycosuria and again acquired an entirely normal blood-sugar curve. As long as obesity was avoided such patients were by all criteria non-diabetic; if weight increased diabetes returned. It seemed reasonable to suppose that if such patients had never become obese they would not have developed diabetes, and it was accordingly suggested that food rationing, by reducing the weight of, and by preventing obesity in, potential diabetics, had, inadvertently, reduced the incidence of diabetes in general in the country.