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The inheritance of liability to diseases with variable age of onset, with particular reference to diabetes mellitus

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INTRODUCTION

In a previous paper (Falconer, 1965) I proposed a method of genetic analysis for diseases with multifactorial inheritance which leads to an estimate of the heritability of liability to the disease. The present paper will first point out an erroneous assumption that makes the method unreliable when applied to twins. The main purpose of the paper, however, is to show that one restrictive condition made in the previous paper is unnecessary. With this condition removed, the analysis will be developed in a more adequate manner than was done previously for diseases with variable age of onset and incidence increasing with age. The analysis will then be applied to published data on diabetes mellitus. The premisses on which the method described in the previous paper is based are, very briefly, as follows. All the causes, both genetic and environmental, that make an individual more or less likely to develop the disease can be combined into a single measure called the individual's 'liability'. The liabilities of individuals in a population form a continuous variable. The apparent discontinuity between affected and normal arises from a 'threshold' at some level of liability. Individuals with liabilities above the threshold are affected and individuals with liabilities below it are not. In practice the distinction between affected and normal must be based on diagnosis. Therefore the factors that influence the stage in the development of a disease at which an individual is diagnosed are part of his liability and contribute to the variation of the liability among individuals. The liability of an individual cannot be measured, but the mean liability of the population or group can be evaluated from the incidence of the disease in that population or group. For this it must be assumed that liability can in principle be expressed in units on a scale that renders its distribution normal. The units of measurement of the mean liability are then standard deviations on this scale. The analysis provides an estimate of the correlation between relatives in respect of liability, and this leads, with certain assumptions, to an estimate of the heritability of liability in the population. The heritability is the proportion of the variance of liability that is ascribable to additive genetic variance. This is the nearest one can get with the human data to the degree of genetic determination of liability. The data required for the analysis are the incidence of the disease in the population and the incidence in relatives of affected propositi drawn from the population.

The term 'incidence' was used in the previous paper with the meaning that in epidemiology would be termed 'prevalence', and for the sake of consistency I shall continue to use 'incidence' in this paper. By 'incidence' I mean the frequency of affected individuals; i.e. the proportion of living individuals found to be affected in the population, or among the relatives. The incidence in a particular age-group is the proportion of people in that age-group who have the disease, irrespective of the age of onset.

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Assumption of normality

The method is based on the assumption that liabilities are normally distributed in the relatives of affected propositi, as well as in the population as a whole. I am grateful to Dr J. H. Edwards for pointing out that, if liability is normally distributed in the general population, which is part of the definition of liability, then it will not be normally distributed in the relatives of affected propositi. The reason is as follows. The affected individuals are the truncated upper tail of the normal distribution of the general population, and their phenotypic liabilities are therefore very far from normally distributed. If liability is to some degree inherited the genetic levels of liability in the affected individuals will not be normal. Consequently the relatives of the affected individuals will also have liabilities that are not normally distributed. The error introduced by assuming the relatives to be normally distributed is usually very small and can safely be neglected. Experiments with laboratory animals show that, when the individuals in the upper tail of a normal distribution are selected and bred from, the distribution in their offspring does not differ detectably from normality. So it is safe to ignore the error when the heritability of liability is being estimated from first degree, or more distant, relatives. But, if monozygotic twins are used, and the heritability is high, the error is large enough to make the method invalid. I am indebted to Dr I. I. Gottesman for pointing out the serious consequences of this error when the method is applied to twins. The consequence of the error is to make the estimate of the heritability too high. For example, an incidence (concordance rate) of about 65 % in monozygotic twins leads to an estimate of 100 % for the heritability. This obviously could not be right because if the heritability were 100 % the concordance rate in monozygotic twins could not be below 100 %. It should be possible to modify the method so as to overcome this error, but here I only want to point out that if applied to twins the method must be expected to give erroneously high estimates of the heritability.

Differences of variance

In the previous paper I said that it was necessary to assume that the variance of liability was the same in any two groups compared; for example, in comparing males with females, or one age-group with another. This restrictive assumption proves to be unnecessary because the method of analysis automatically makes the required adjustment in the calculation of the heritability. This fact, which was pointed out to me by Dr C. Smith, is important in the development of the method for diseases with age-dependent incidence, and so it will be explained in some detail.

If the incidence of the disease differs in the two sexes, or in two different age-groups, this difference of incidence can be ascribed to a difference of mean liability, or to a difference of the variance of liability, or to a combination of both. Fig. 1 illustrates the two simple alternatives. It shows the distribution of liability in two groups, 1 and 2, with a higher incidence in group 2 than in group 1. In Fig. 1*a* the means differ but the variances are the same, while in Fig. 1*b* the means are the same but the variances differ. The analysis in the previous paper was based on the assumption of equal variances, as in Fig. 1*a*. The scale of liability was in standard deviation units and these were equal for the two groups. If we make no assumption about the equality of either the variance or the mean, we cannot use the standard deviation as a scale unit because the standard deviations may be different in the groups being compared. We have therefore to imagine an 'absolute' scale of liability, such as we should use

if we could measure the liability of individuals directly. This scale is the same for all groups, and all the distributions in Fig. 1 are drawn in proportion to it, though the units are not shown in the figure. If m_1 and m_2 are the means of the two groups, measured in absolute units as deviations below the threshold, then

$$\left.\begin{aligned} m_1 &= x_1\sigma_1 \\ \text{and} \quad m_2 &= x_2\sigma_2, \end{aligned}\right\} \tag{1}$$

where x is the normal deviate (derived from the incidence, and tabulated in the previous paper) and σ is the standard deviation.

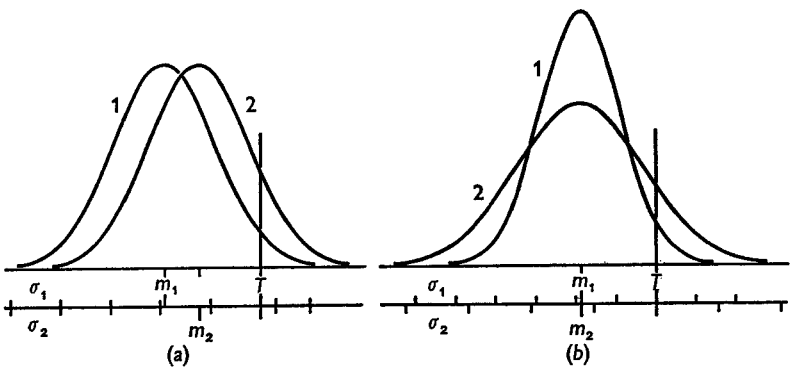

Fig. 1. Differences of incidence caused by (*a*) a difference of mean liability with equal variances, and by (*b*) a difference of variance with equal means.

Now consider the calculation of the regression of relatives on propositi when relatives and propositi belong to different groups: for example, the regression calculated from the female relatives of male propositi. Equation (5) of the previous paper gave the following expression for the estimation of the regression:

$$b = (x_{gr} - x_r)/a_g.$$

The subscripts r and gr refer respectively to the relatives and the general population of the group to which the relatives belong; a_g is the deviation of affected individuals from the mean of the population of the group to which the propositi belong. Let the propositi be drawn from group 1 with standard deviation σ_1, and let the relatives belong to group 2 with standard deviation σ_2. The regression coefficient expressed in absolute units (denoted by b') will then be given by

$$\begin{aligned} b' &= (x_{gr}\sigma_2 - x_r\sigma_2)/a_g\sigma_1 \\ &= [(x_{gr} - x_r)/a_g]\,(\sigma_2/\sigma_1), \end{aligned}$$

whence

$$b = b'(\sigma_1/\sigma_2).$$

Thus the regression, b, estimated by equation (5) of the previous paper is the 'standardized' regression coefficient, and this is equal to the correlation coefficient. Consequently, if the propositi and relatives belong to groups with different variances, the method given in the previous paper will correctly estimate the correlation between the relatives of the sort under consideration; and it will estimate $b'(\sigma_1/\sigma_2)$, where b' is the regression coefficient in absolute units, and σ_1 and σ_2 are the standard deviations of the groups to which propositi and relatives respectively belong.

The relationship between the regression coefficient in absolute units, b', and the heritability, h^2, is as follows:

$$b' = rh_1h_2r_G(\sigma_2/\sigma_1),$$

where r is the coefficient of relationship ($\frac{1}{2}$ for first-degree relative), h_1 and h_2 are the square roots of the heritabilities in the population from which the propositi and the relatives respectively are drawn (e.g. heritability in males and in females respectively), and r_G is the genetic correlation expressing the extent to which liability is affected by the same genes in the two groups. (The proof of this relationship is too lengthy to be given here; it can be derived fairly simply from equation (19.5) in Falconer, 1960, p. 318.) Substituting b for b' in the above equation leads to

$$b = rh_1h_2r_G. \tag{2}$$

If the two heritabilities are the same and the genetic correlation is unity, then, for first-degree relatives, $h^2 = 2b$, which is the relationship given in the previous paper. Thus we can correctly apply the equations given for the calculation of the heritability, even if the variances of the groups compared may differ. There is, however, one qualification that must be made: if the variances do differ, the difference is more likely to be in the environmental than in the genetic component. A difference of variance is therefore likely to entail a difference of heritability, and equation (2) above should be applied when the data are sufficient to justify the calculation of the two heritabilities separately. To assume that the genetic correlation, r_G, is unity will probably not introduce much error when the difference between relatives and propositi is one of sex. When the difference is in age, however, the estimation of the genetic correlation, which equation (2) makes possible, may be very important, because it will indicate the extent to which different ages of onset represent different genetic causation. This point will be elaborated in a later section.

Age-dependent incidence

If the incidence of a disease in the general population is greater among older age-groups than among younger, the increased incidence can be attributed to an increase of mean, as illustrated in Fig. 1*a*, or to an increase of variance, as in Fig. 1*b*, or to both combined. The foregoing section showed that the cause of the increased incidence does not affect the calculation of the heritability of liability, and relatives do not have to be of the same age as propositi.

It is worth while to consider in more detail how an increase of mean or an increase of variance might take place, by picturing the way in which individual liabilities change with increasing age. This will show more clearly what additional conclusions may be drawn from the estimation of the heritability in different age-groups. The ways in which individual liabilities may change so as to give rise to an increasing incidence can be depicted in the following 'models' illustrated in Fig. 2.

Model I. Mean liability increases; variance remains constant (Fig. 2*a*). Under this model all individuals would increase in liability at the same rate. This is a necessary consequence of supposing the variance to remain constant. Liability would therefore be completely correlated with age, and the increase of liability would have to be regarded as an inevitable aspect of the 'ageing' process. Since there is no change of variance the heritability would be the same in all age-groups. By supposing the variance to remain constant this model denies the existence of environmental sources of variance that affect liability after birth or after an early age. It is therefore a very unrealistic model and is untenable for diseases such as peptic ulcer or diabetes.

The normal centroids for $2n = 10$ are $\pm 1{\cdot}75498$, $\pm 1{\cdot}04464$, $\pm 0{\cdot}67731$, $\pm 0{\cdot}38650$, $\pm 0{\cdot}12600$. If we replace the ranks by these normal centroids the mean of the centroids of the observed sample is 0·0455 and the number in the set having a value as large or larger than this is 50 %.

6. *Ties*

Where two or more observations have the same value there is no alteration in the randomization procedure with the variate values. For the ranks transformation all tied values are given the same (mid) rank and similarly for the normal centroids. If many observations are tied it will be preferable to calculate the actual variance instead of using the formulae given.

7. *The case for s tests*

We now suppose that there are n patients each subjected to a set of s tests before and after treatment. Let the difference of the scores of the ith patient in the jth test before and after be d_{ij} $(i = 1, 2, \ldots, n;\ j = 1, 2, \ldots, s)$. Construct a complementary set of differences for each test by changing the sign of d_{ij} so that there will be s sets each of $2n$ differences. For each set we replace the differences by normal centroids and we suppose that we have U_{ij} $(i = 1, 2, \ldots, 2n;\ j = 1, 2, \ldots, s)$. Let the centroids of the observed sets of differences, which are contained in the U_{ij}, be denoted by X_{lk} $(l = 1, 2, \ldots, n;\ k = 1, 2, \ldots, s)$ with

$$\bar{X}_k = \frac{1}{n} \sum_{l=1}^{n} X_{lk}.$$

Of necessity

$$\bar{U} = \frac{1}{2n} \sum_{i=1}^{2n} U_{ij} = 0$$

and we shall assume n large enough to allow us to take

$$\sigma_j^2 = \frac{1}{2n} \sum_{i=1}^{2n} U_{ij}^2$$

equal to unity. There will be a correlation between U_{ij} and U_{ik} if for no other reason than that they relate to the jth and kth tests carried out on the same (ith) person. We denote this correlation by

$$\rho_{jk} = \frac{1}{2n} \sum_{i=1}^{2n} U_{ij}\, U_{ik},$$

and the correlation matrix by R, where

$$R = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} & \cdots & \rho_{1s} \\ \rho_{12} & 1 & \rho_{23} & \cdots & \rho_{2s} \\ — & — & — & — & \cdots \\ \rho_{1s} & \rho_{2s} & \rho_{3s} & \cdots & 1 \end{bmatrix}.$$

R_{ij} will denote the signed minor of the determinant $|R|$ of R. By analogy with the likelihood ratio tests generated for the multivariate normal distribution, the criterion to test the hypothesis of no improvement in the patients (due to treatment) will be (David & Fix, 1960):

$$\mathscr{T} = \frac{n}{|R|} \left\{ \sum_{j=1}^{s} R_{jj}\, \bar{X}_j^2 + \sum_{j \neq l} R_{jl}\, \bar{X}_j\, \bar{X}_l \right\}.$$

We have that

$$\mathscr{E}\mathscr{T} = s; \quad \mathscr{E}\mathscr{T}^2 = s(s+2)\frac{(n-2)}{n}; \quad \text{var.}\mathscr{T} = 2s - \frac{2s(s+2)}{n}.$$

sources of variance are allowed so that the variance also increases. It is constancy of variance that makes model I by itself so improbable.

Model IV. Both mean and variance increase (Fig. 2*d*). There is another way in which both mean and variance might increase. The changes of individual liabilities throughout life might be in the upward direction only. This would happen if the disease were associated with damage to tissue. Adverse environmental factors might cause damage which was not subsequently repaired, and each damaging event might raise the liability towards the threshold level. These environmental factors would add to the variance of liability in later ages and the heritability would decline. This model seems possible for some diseases, particularly diabetes. It is attractive because the increase of mean and of variance both arise from a single cause, namely environmental events.

Consideration of the causes that might lead to an increase of incidence, in terms of the foregoing 'models', shows that we must expect an increase of variance with advancing age. Furthermore, the additional variance is most likely to be environmental, so that we must expect to find heritabilities declining with advancing age. There are also experimental grounds for expecting an increase of environmental variance with increasing age. Storer (1965) reported increases of non-genetic variance with increasing age in six measurements associated with physiological processes in mice, the increase of variance being attributed to the impairment of homeostatic mechanisms with advancing age.

Heritability at different ages

What does it mean to say that the heritability changes as people grow older? Suppose we take all the people of a particular age, say 40, from the population. Some of these will be affected and they will have some relatives, also aged 40. From the incidence in the total population aged 40, and in the relatives of the affected propositi, we calculate the heritability at age 40 and find it to be, say, 30 %. This means that the differences of liability among people aged 40 are heritable to the extent of 30 %. Now suppose that we look in the same way at people aged 60, and find the heritability of liability at 60 to be 20 %. The differences of liability are now heritable to the extent of only 20 %. Consequently, between the ages of 40 and 60 environmental circumstances have increased the non-genetic differences of liability between individuals.

If the heritability is calculated from relatives of the same age as the propositi, this is the heritability (h^2) at that age. If, on the other hand, the propositi are of age 1 and the relatives of age 2, then the estimate calculated from the regression (by equation (2) above) is of $h_1 h_2 r_G$. If the heritabilities at the two ages, h_1^2 and h_2^2, are first calculated from relatives of the same age as the propositi, it should therefore be possible to estimate r_G, the genetic correlation between liability at the two ages. This will throw light on the question whether liability at different ages is to any extent influenced by different sets of genes.

Relationship between heritability and incidence. If model II is the correct one—i.e. the increase of incidence is due entirely to an increase of environmental variance, then the expected reduction of the heritability can easily be calculated. A comparison of the expected with the observed change of heritability associated with the increase of incidence will then show whether the data are consistent with model II or not. If the heritability declined less than would be expected from an increase of environmental variance alone, we should have to conclude that

the mean liability had also increased, or (less probably) that the genetic as well as the environmental variance had increased. The test of agreement with model II can conveniently be made as follows.

Let m be the mean in absolute units, and σ the standard deviation, at any particular age; and let x be the normal deviate corresponding to the incidence at this age. Then, by equation (1),

$$x = m/\sigma. \tag{3}$$

Note that σ is the phenotypic standard deviation, so that σ^2 is the phenotypic variance. The heritability, h^2, is by definition the ratio of the additive genetic variance to the phenotypic variance, i.e.

$$h^2 = \sigma_G^2/\sigma^2, \tag{4}$$

where σ_G^2 is the additive genetic variance. Dividing equation (3) by the square root of equation (4) leads to

$$x/h = m/\sigma_G. \tag{5}$$

Thus, by dividing the value of x at any age by the square root of the heritability at that age, we get a measure of the mean liability in units of *genetic* standard deviations. This contrasts with (3), where the value of x gives a measure of the mean in units of *phenotypic* standard deviations. (The sign, or direction, of m in (3) and (5) is apt to be confusing. Since m is defined as a deviation *below* the threshold, a reduction in the numerical value of m signifies an increase of mean liability. Therefore a reduction in the numerical value of m/σ or m/σ_G would be caused by either an increase of the mean liability or an increase of the standard deviation.)

By comparing the changes with age shown by (3) and by (5) we can draw the following conclusions. If m/σ_G does not change with age, the increase of incidence can be fully accounted for by an increase of environmental variance only, and the data would be consistent with model II. If m/σ_G does change, an increase of environmental variance alone is not sufficient to account for the increase of incidence, and there must have been also an increase of mean liability or an increase of genetic variance, but it is not possible to discriminate between these two.

Age of onset. If the incidence increases with advancing age there must be variation in the age of onset among affected individuals. Several interesting questions might be asked about the age of onset; for example, to what degree is it inherited? Is it correlated with liability? To what extent are age of onset and liability separately inherited? The ways in which these questions might be answered will not be discussed here, however, because the questions are rather more complicated than they may appear, and because the data on diabetes to be analysed do not contain the information needed to answer them.

Grouping by age. There are one or two points of a relatively minor nature in connexion with the grouping of the data to which attention must be drawn. In order to obtain sufficient data for the estimation of the various parameters at different ages it is obviously necessary to group the ages in intervals of five, ten, or more years. If the heritabilities at different ages are to be computed, it is necessary to know the ages of both the propositi and the relatives, and to have them grouped by age in the same way. There are three ways in which the grouping can be done, depending on the method of ascertainment, and these have slightly different consequences for the analysis. First, the affected propositi may be a random sample from the population or from patients registered at the clinic. In this case the appropriate analysis is by the formulae given in the previous paper (Falconer, 1965). Secondly, the affected propositi

may be patients at their first attendance at a clinic. Their present age is therefore their age of onset, i.e. at diagnosis, and their liability is, by definition, at the threshold. Their mean deviation from the population mean is therefore given by x instead of by a, and x should be used in the place of a in the formulae. With both these methods of ascertainment grouping will be by the present age of the propositi, and people in different age-groups will belong also to different cohorts; present age and date of birth will consequently be completely correlated negatively. Therefore any difference of mean liability, or of the heritability between different age-groups, may equally well represent a difference between age-groups or between cohorts. A third method of grouping would allow the effects of age and cohorts to be separated, but it requires knowledge of the age of onset of affected propositi and of the affected relatives. If the age of onset is known, all the individuals give information for their own cohorts about the incidence at all ages before their present age. Comparisons can then be made between people of the same age but belonging to different cohorts. For example, a group now aged 30–40 can be compared with a group who were aged 30–40 twenty years ago. In this way changes associated with chronological date can be separated from changes associated with age. Knowledge of the age of onset has another advantage because it allows the heritability to be calculated for a precise age instead of for an age-group. The heritability at age 40, for example, would be based on propositi (aged 40 or more) who were affected at 40 (i.e. age of onset before 41), and the proportion of their relatives (aged 40 or more) that was affected at 40.

DIABETES MELLITUS

There is now strong evidence that the inheritance of diabetes mellitus is multifactorial (Bigozzi & Teodori, 1965; Neel, Fajans, Conn & Davidson, 1965; Thompson, 1965; Clarke, 1966). The estimation of the heritability of liability is therefore the appropriate method of genetic analysis for diabetes. Moreover the concept of the underlying variability—the liability —is more clearly valid than for probably any other disease. Since the blood glucose level forms the basis of diagnosis this measurement must be closely correlated with liability; and its variation is continuous, with no clear demarcation between the normal and the abnormal. When familial incidences are to be used for genetical analysis, however, the criterion of abnormality is not the blood sugar level but the recognition of diabetes. The liability then includes not only the blood sugar level but also the other factors that influence the recognition of the disease. These include the mainly accidental event of a routine urine test, and the mainly psychological factor of readiness or reluctance to consult one's doctor. Therefore in an analysis of records of 'known diabetics' some of the diabetic individuals will have lower blood sugar levels than some individuals recorded as non-diabetic, and the blood sugar level will not be completely correlated with the liability.

It is not my object here to attempt a comprehensive discussion of the genetics of diabetes, but simply to apply the analysis elaborated in this paper to the published data on familial incidences, and see what conclusions can be drawn about the changes associated with advancing age.

The data. I have applied the analysis to two sets of published data. One set of data (Simpson, 1964) was obtained from a questionnaire sent to known diabetics in Canada. The familial incidences include sibs, parents, and children. The incidences in male and female relatives are given separately and the relatives are divided into 10-year age-groups; but the propositi are

not separated by sex and their ages are not given. The general population, in which the incidence is given by 10-year age-groups, is as representative of the population to which the propositi belonged as could be obtained. The other set of data (Diabetes Survey Working Party, 1965) refers to the population in or near Birmingham, England. The propositi were patients at their first attendance at a clinic in 1961 and 1962, and there was also a control group of non-diabetic propositi matched for age and sex with the diabetic propositi. The general population incidences come from a survey in the same area (Diabetes Survey Working Party, 1962). Only known diabetics found in the survey are counted in the incidences. The familial incidences include sibs and parents and are grouped according to the age of the propositi, but the ages of the relatives are not given. The incidences are all given in four age-groups, but are not separated by sex.

Liability and age. The population incidences in the different age-groups, and the corresponding values of x (the normal deviate), are given in Table 1. The values of x for the two sets of data are plotted in Fig. 3*a*. From equation (1), x is a measure of m/σ, where m is the mean liability and σ is the standard deviation of liability. Since m is measured as a deviation below the threshold, a decrease in the numerical value of x indicates an increase of either the mean or the variance. The graphs are plotted so that an upward trend indicates an increase of mean or variance. Both sets of data show a regular increase of mean liability, or of the variance of liability. The males in the Canadian data show an almost exactly linear increase up to the age of 55. The females have a somewhat lower liability (or variance), which increases at the same rate as the males up to age 45. Between 45 and 55, however, the females increase more steeply, corresponding to the well-known increase of incidence associated with obesity in older women. The levelling off of the graphs above the age of 60 or 70 suggests that there is no further increase of mean liability or of variance above this age. But the levelling off may be, at least partly, due to selective mortality. People in their 70's at the time of the survey would have been in their 30's when insulin was introduced, so cases with early onset will probably be missing from this age-group. The Birmingham data, in which the sexes are combined, also show a regular increase but at a slower rate than in the Canadian data, and they do not show the same levelling off in the oldest group. The linear relationship between x and age, incidentally, makes it possible to supply missing values with some confidence. For example, in the Canadian data there were no affected males in the 20–29 age-group, and no affected females in the 0–9 and 10–19 age-groups. It is clear that these zero incidences are accidents of sampling, and more realistic values can be supplied by interpolation or, though less reliably, extrapolation from the graphs of x. The values of x estimated in this way, which are used for these age-groups in the calculation of the heritabilities, are shown by small dots in the graphs, and the corresponding incidences are given in Table 1.

Sib correlation of liability. To estimate the heritability at any particular age it is necessary to have both propositi and relatives of the same age. Though in neither set of data are the ages of both propositi and relatives given, it may be assumed that sibs were approximately the same age as propositi. With this assumption, the incidence in the sibs of affected propositi can be used to estimate the heritability of liability at different ages. It must be remembered, however, that the estimation of the heritability from the correlation between sibs is unreliable because environmental causes of resemblance are likely to be particularly important, and the resemblance may be increased also by non-additive genetic variance. The estimates of the

heritability must therefore be regarded as suspect until they can be confirmed from other relatives, but the correlation is not open to these objections and is reliable within the limits of the sampling errors.

Table 1. *Incidences of diabetes mellitus by age-group in the general populations*

(q is the incidence, x is the normal deviate and measures m/σ, where m is the mean liability and σ is the standard deviation of liability. The values in parentheses are estimated from the graphs in Fig. 3*a*, the observed incidences being zero.)

Canadian data					Birmingham data		
Males			Females				
Age-group	q (%)	$x \pm$ S.E.	q (%)	$x \pm$ S.E.	Age-group	q (%)	$x \pm$ S.E.*
0–9	0·037	3·38 ± 0·27	(0·018)	(3·58) —	0–29	0·2	2·89 ± 0·16
10–19	0·067	3·21 ± 0·20	(0·034)	(3·40) —			
20–29	(0·186)	(2·90) —	0·095	3·11 ± 0·21			
30–39	0·475	2·59 ± 0·12	0·248	2·81 ± 0·14	30–49	0·4	2·65 ± 0·10
40–49	1·110	2·29 ± 0·09	0·566	2·53 ± 0·11			
50–59	2·231	2·01 ± 0·08	2·596	1·94 ± 0·07	50–59	1·3	2·23 ± 0·06
60–69	2·456	1·97 ± 0·09	4·469	1·70 ± 0·07			
70–79	3·899	1·76 ± 0·10	4·100	1·74 ± 0·08	70+	2·1	2·03 ± 0·05
80+	3·428	1·82 ± 0·18	2·360	1·98 ± 0·15			

* The numbers affected, on which the standard error is based, are not given but were deduced (approximately) from the graphs in the Diabetes Working Party (1962).

The heritabilities of liability at different ages in the two sets of data, obtained by doubling the sib correlation, are given in Table 2 and are plotted in Fig. 3*b*. The correlations in the Canadian data and their standard errors were calculated from the formulae given under method 1 in appendix B of Falconer (1965). Since the propositi are not separated by sex it was assumed that there were equal numbers of males and females: the value of a used in the computations was the value corresponding to the mean of the values of x for males and x for females in that age-group. The calculation of the Birmingham data was made by method 4 because the relatives of patients were compared with a control group rather than with the general population. A slight modification of the formula was required because the propositi were newly diagnosed cases. From the definition of the threshold, the liability of each proposita was at the threshold, and the mean deviation of propositi from the population mean is to be taken as x and not as a. The correlation is therefore estimated as

$$p_g(x_c - x_r)/x_g,$$

and the variance of this estimate is given by

$$\left[-b\left(\frac{1}{x} - \frac{aq}{p}\right)\right]_g^2 W_g + \left[\frac{p}{x}\right]^2 [W_c + W_r],$$

where the symbols have the meaning given in Falconer (1965).

The two sets of data show a consistent picture. The heritability drops from a high value of about 70 % or 80 % in young people to about 30 % or 40 % in people over 55. This shows that older people are subject to environmental sources of variation that are not present in young

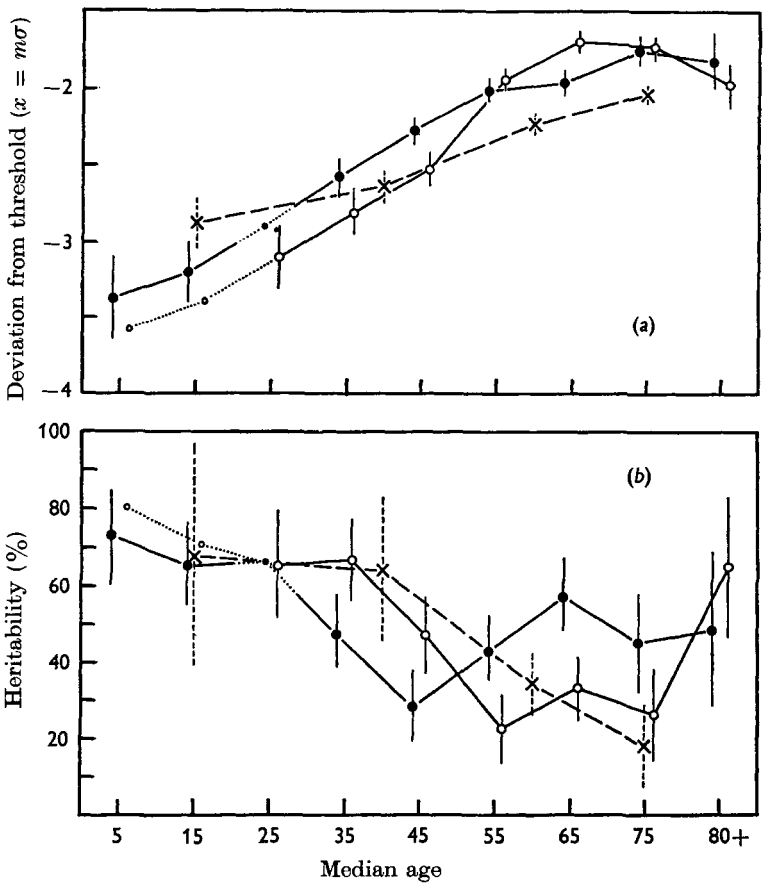

Fig. 3. Diabetes mellitus: changes with increasing age. (*a*) Mean liability in standard deviation units. The changes can be interpreted as either an increase of the mean liability or an increase of the variance of liability (see text). (*b*) The heritability of liability estimated from the sib correlations. ● —— ●, Canadian data, males; ○ —— ○, Canadian data, females; × — — ×, Birmingham data, both sexes combined. The vertical lines extend to ± one standard error.

Table 2. *Heritability of liability to diabetes mellitus at different ages, obtained by doubling the sib correlation*

(The sexes separated in the Canadian data refer to the relatives.)

Canadian data			Birmingham data	
	Heritability (% ± S.E.)			
Age-group	Males	Females	Age-group	Heritability (% ± S.E.)
0–9	73 ± 13	81 ± *	0–29	68 ± 29
10–19	66 ± 11	71 ± *		
20–29	67 ± *	65 ± 14		
30–39	47 ± 10	67 ± 11	30–49	64 ± 19
40–49	29 ± 9	47 ± 10		
50–59	43 ± 9	22 ± 9	50–69	34 ± 8
60–69	58 ± 10	33 ± 9		
70–79	44 ± 13	26 ± 12	70+	18 ± 11
80+	48 ± 21	65 ± 19		

* Standard errors not known because the general population incidence was estimated from the graph, as explained in the text.

people and that do not tend to affect members of a family alike. The high sib correlation in young people, however, may indicate similarity of environmental circumstances rather than a high heritability. This point will be discussed further later.

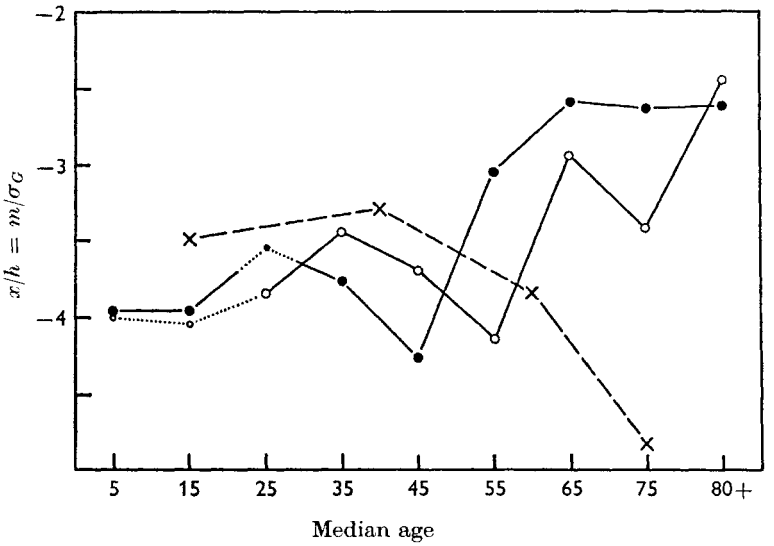

Fig. 4. Diabetes mellitus: mean liability in units of genetic standard deviations. Explanation in text. Symbols as in Fig. 3.

So far, then, the data show that there is an increase of environmental variance with advancing age, and that at least some of the increasing incidence must be attributed to an increase of variance. The next point to examine is whether the increase of incidence and the reduction of heritability are consistent with an increase of environmental variance alone, without any change of the mean liability. This can be tested, though not unequivocally, by seeing whether the ratio x/h is constant or not. This ratio (equation (5) above) expresses the mean liability in terms of the genetic standard deviation, which, though not necessarily constant, is more likely to be constant than the phenotypic standard deviation. The values of $x/h = m/\sigma_G$ are plotted in Fig. 4. The Canadian data show a definite increase, more marked in the later age-groups. This means that the increase of incidence is too great to be accounted for by an increase of environmental variance alone, and the mean liability must also have increased with age. The data therefore do not fit models I or II described above, but are consistent with models III or IV, in which both the mean liability and the variance increase with age. The Birmingham data on the other hand show a reduction of x/h, particularly in the 70+ age-group. This reduction seems likely to be an error of sampling because if true it would indicate a reduction of mean liability, which seems very improbable. It could, however, be due to a spuriously low incidence in the 70+ age-group resulting from differential mortality. Or, since age and date of birth are completely correlated, it could be taken to indicate a lower mean liability in people born before about 1890 (i.e. the approximate date of birth of the 70+ group in 1961) than in people born later. A lowering of the threshold, which is equivalent to an increase of the mean liability, in the current generation has been suggested by Neel *et al.* (1965) as a possible explanation of some of their results. Any change of mean liability that may have taken place over a time span must have been environmentally caused, since genetic changes would be too slow to be detectable.

An increase with age of both mean liability and of the variance of liability, as shown by the Canadian data, is consistent with the changes of blood sugar levels reported by the Diabetes Survey Working Party (1963). Blood glucose levels were measured on 345 control subjects when fasting and at 1 and 2 hr. after a 50 g. glucose load. Both the mean and the standard deviation increased with increasing age. The increase of the mean was most marked in the 1 hr. measure. In all three measures the standard deviation was approximately twice as great in the 70+ age-group as in the 0–29 group. Neel *et al.* (1965) also found that both the mean and the variance of the blood sugar level increased with age. In this case the subjects, who were controls with no family history of diabetes, were tested 2 hr. after a 100 g. glucose load. The standard deviation of the blood sugar level was $1\frac{1}{2}$ times as great in the 60+ age-group as in the 20–29 group. Thus the relationship between liability and age disclosed by the analysis of the Canadian data accords well with the directly observed changes of blood sugar level. This supports the idea that the glucose tolerance test is a measure that is closely correlated with liability.

Parents and children, age ignored. Because of the uncertainty mentioned earlier about the contribution of environmental factors to the correlation between sibs, it is very desirable to have estimates of the heritability from other relatives for comparison. The Canadian data include incidences in parents and children, and the Birmingham data include the incidence in parents. It will not be worth while to calculate the liabilities separately for each age-group because parents and children necessarily differ in age from propositi, and the ages of either the propositi (in one set of data) or of the relatives (in the other set) are not known; the correlation between relatives of one age and propositi of all ages, or vice versa, would be hard to interpret in terms of heritabilities. It is worth while, however, to calculate the heritabilities from all ages pooled. This will give an overall picture of the heritability in the whole population with its particular age distribution. Calculated thus, the estimates from different sorts of relatives should be substantially the same, and this provides a test of whether the correlation between sibs is substantially inflated by environmental similarity. The overall heritability calculated from all ages pooled should correspond more closely with that in older rather than in younger people because the majority of affected propositi belonged to the older groups. Furthermore, the overall heritability should be somewhat lower than the weighted average heritability within age-groups, because any effect of age on mean liability is included as a source of non-genetic variation when all ages are pooled.

The estimates of the overall heritabilities from all the different relatives in the two sets of data are given in Table 3, and the average ages are given in Table 4. The estimates from the Canadian data were calculated by method 3 of Falconer (1965). The value of x_r was taken from the overall incidence in the relatives, and of x_{gr} from the 'expected' incidence, i.e. the incidence in the general population adjusted to the age distribution of the relatives (with the 'missing values' supplied as explained earlier). The value of a_g was taken from the mean value of x for males and x for females in the general population. The estimates from the Birmingham data were calculated in the same way as was described for the separate age-groups. In the Canadian data there are some children of diabetic propositi married to diabetic spouses. The heritability is estimated from these as the correlation itself, instead of twice the correlation.

The agreement between the estimates of the heritability from the different sorts of relatives is very satisfactory in both sets of data, and the agreement between the two sets of data is also

very close. When the estimates from sibs are compared with those from parents and children there are some grounds, though they are not very strong, for thinking that the sib correlation may be inflated by environmental similarity to a greater extent than that between parents and children. Male sibs in the Canadian data give an estimate (41 %) which is substantially higher than that from male parents and children (32 %), but the difference is not significant and neither the female sibs in the Canadian data nor the sibs in the Birmingham data give estimates that are much higher than those from parents and children. There is therefore some indication of environmental similarity between sibs though it is not proved. The younger ages are, however, not well represented in the overall data, so the very high correlation between sibs found in the younger age-groups may still be due to environmental factors.

Table 3. *Diabetes mellitus: heritability of liability* (% ± S.E.) *from all ages pooled*

	Overall heritability	
	Sex of relatives	
Relatives	Male	Female
Canadian data		
Sibs	41 ± 3	31 ± 3
Parents	31 ± 5	26 ± 5
Children (1)*	32 ± 7	35 ± 7
Children (2)*	34 ± 9	29 ± 11
Parents and children, weighted mean	32 ± 4	29 ± 4
Birmingham data		
Sibs	35 ± 6	
Parents	34 ± 6	
Weighted average heritability within age-groups, from sibs†		
Canadian data	50	47
Birmingham data	38	

* (1) One parent diabetic, i.e. the propositus. (2) Both parents diabetic, one being the propositus.
† From Table 2, weighted by the total number of relatives in the age-group.

Table 4. *Approximate mean ages of the general populations and of the various relatives, sexes averaged*

(The greatest difference between the sexes was 4 years.)

Canadian data	years
General population	32
Diabetics in general population	60
Relatives of propositi	
Sibs	44
Parents	57
Children (1)	25
Children (2)	33
Birmingham data	
General population (survey)	37
Known diabetics in survey	64
Propositi*	55

* Assuming the number of propositi in each age-group to be proportional to the number of relatives recorded.

The comparison between the overall heritability from sibs and the heritability within age-groups, shown at the foot of Table 3, comes out as expected, the overall heritability being lower. The difference is less marked in the Birmingham data but this again is to be expected because

the age-groups are wider and there would be more non-genetic variance associated with age within the groups.

Taking all relatives together, from both sets of data, the overall heritability of liability comes out at about 35 %. This is about the same as was found for peptic ulcer (Falconer, 1965), and cannot be regarded as a very high value. In the population as a whole, therefore, liability to diabetes is not very highly inherited, differences between individuals being inherited to the extent of about one-third. Among young people, however, the heritability may be very much higher.

Early onset. Simpson separates out from the Canadian data propositi whose age of onset was before 20 years, and gives the incidence in their sibs, parents and children grouped by age. We have here, therefore, a group of propositi who were affected at the age of 20, and their relatives in various age-groups, and so we know the ages both of the propositi and of the relatives. The numbers of relatives are not large enough to justify treatment of each age-group separately, so all ages of relatives have been pooled, except that sibs aged less than 20 are shown separately. It was also necessary to pool male and female children. The 'heritabilities' obtained from the propositi with onset before 20 are given in Table 5, and the interpretations of these in terms of the heritabilities at different ages and the genetic correlation are also given.

The estimates from the sibs agree well with those obtained previously when the propositi were of all ages, and this shows that not much error was introduced by the assumption that the propositi were of about the same age as their sibs. The children of propositi with onset before 20 give an estimate that is considerably lower than that obtained from sibs of comparable age, 52 % in place of 75–80 %. This suggests that the high sib correlation in young people is partly due to environmental similarity. Unfortunately, however, the standard error is very large and there is little justification for drawing this conclusion.

The most interesting aspect of the data from propositi with onset before 20 is the information they give on the question of whether cases with early onset are genetically different from cases with later onset. This information comes from the parents, who had an average age of 48. Doubling the correlation between parents and propositi therefore gives an estimate of $h_{20}h_{48}r_G$ (equation (2)), where r_G is the genetic correlation between liability at 20 and liability at 48. The genetic correlation provides a measure of the extent to which liability at the two ages is determined by the same genes. The estimates of $h_{20}h_{48}r_G$ are 0·20 from fathers and 0·07 from mothers. There is some doubt as to whether the relatively low incidence in these parents is reliable because, as Simpson (1964) points out, cases with early onset may be missing as they would have died young before the use of insulin. If this possible error is discounted, these estimates suggest that the genetic correlation is considerably less than unity, for the following reason. To estimate r_G we have to know the heritabilities at the ages of 20 and 48. The heritability at age 48 (h^2_{48}) can be assumed to be well enough estimated from the sibs analysed earlier (Table 2 and Fig. 3*b*), on the grounds that at this age environmental similarity between sibs is likely to be relatively unimportant. From the graph in Fig. 3*b*, h^2_{48} can be taken as 40 % in males and 30 % in females. For the heritability at age 20 (h^2_{20}) we cannot confidently take the value obtained from sibs because of the possible inflation of environmental similarity. But we can take two extreme values and so obtain upper and lower limits for the genetic correlation. An upper limit for h^2_{20} can be taken from Table 5 as 60 % in males and 58 % in females. (These are from propositi with onset before 20 and their sibs of all ages, who had in fact an average age of 20.) As a lower limit, h^2_{20} can be taken to be the same as h^2_{48}. These upper and lower values of h^2_{20} lead to estimates of r_G

of between 0·41 and 0·50 in males, and between 0·17 and 0·23 in females. Thus, unless the incidences in the parents are seriously biased by selective mortality, there is no doubt that the genetic correlation between liability in young people and liability in old people is not unity. Its value cannot be stated precisely but is almost certainly less than 0·5 and perhaps lower in females. This analysis therefore supports the conclusion, tentatively reached by Simpson (1964) and by Harris (1949), that early onset and late onset are to some extent genetically different entities.

Table 5. *Diabetes mellitus: 'heritabilities' (i.e. 2 × correlation coefficient) from relatives of propositi with onset before 20 years of age*

(The mean ages of the relatives are given in parentheses.)

	Sex of relatives		
	Male	Female	
	'Heritability' ± S.E.		'Heritability' is estimate of
Relatives (with mean age)			
Sibs, aged < 20 (10)	0·74 ± 0·12	0·80 ± 0·15	$h_{20}h_{10}r_{G(20.10)}$
Sibs, all ages (20)	0·60 ± 0·06	0·58 ± 0·06	h^2_{20}
Parents, all ages (48)	0·20 ± 0·05	0·07 ± 0·06	$h_{20}h_{48}r_{G(20.48)}$
Children, all ages (8)	0·52 ± 0·16		$h_{20}h_{8}r_{G(20.8)}$

DISCUSSION

Validity of the method

There are some assumptions in the method of analysis presented in this and the previous paper (Falconer, 1965) whose validity may be doubted, particularly those about the form of the distributions of liability, and the assumption that not all human relationships are subject to a large amount of environmental correlation. Little can be gained by discussing the validity of these assumptions individually. The best test of the validity of the method as a whole is the practical one of whether it works; whether, that is to say, the results it gives are consistent with what is known about multifactorial inheritance in general, and also self-consistent when the heritability is estimated in different ways.

All the heritabilities so far estimated are under 100 % and so all are at least possible values. Ranging from about 35 % for diabetes to about 80 % for congenital pyloric stenosis, the values obtained are perhaps higher than might have been expected from experience with laboratory and farm animals, in which the heritabilities of many characters with multifactorial inheritance are known. On the other hand the most directly comparable character studied in laboratory animals that I know of is susceptibility to the induction of lung tumours by urethane (Falconer & Bloom, 1962). The susceptibility, which has the same meaning as liability, had a heritability of 58 % in one strain of mice. This estimate was not obtained by the method under discussion here, but by the well-established method applicable to continuously varying characters. It may well be, therefore, that liability to diseases has heritabilities somewhat higher than we are used to in the characters studied in experimental animals. It is possible also that there is more genetic diversity among human populations than in laboratory or farm animals, so that heritabilities in man may be higher. The differences of heritability between the diseases so far analysed make good sense; the congenital malformations have much higher heritabilities than the diseases developing later in life. This accords well with what we should expect on the grounds that environmental factors will have more effect on diseases of later life.

Self-consistency is the most important test of the validity of the method. This can be looked for in three ways: between the sexes, when the incidence differs; between different sorts of relatives of the same degree; and between relatives of different degrees. The results for diseases with different incidences in males and females were commented on in the previous paper. They were reasonably consistent, and the analysis made sense of what were otherwise very puzzling differences between the incidences in relatives when separated by sex. Some further conclusions about the sex differences can be drawn by applying the development of the method described in this paper. These will be discussed below. The analysis of diabetes in the present paper provides the first comparison of different sorts of relatives. Though this was possible only for all ages pooled, the very close agreement between the heritabilities estimated from sibs, parents, and children showed that the consistency in this respect was very satisfactory. The analysis of diabetes also provided one comparison between relatives effectively of different degrees. This

Table 6. *Comparisons of sexes*

	Peptic ulcer	Congenital pyloric stenosis	Club-foot
From like-sexed relatives			
h_m^2	0·40	0·64	0·59
h_f^2	0·29	0·94	0·69
$h_m h_f$	0·34	0·75	0·64
From unlike-sexed relatives			
$h_m h_f r_G$	0·35	0·87	0·82
Estimate of genetic correlation			
r_G	1·0	1·2	1·3

was the children of two diabetic parents compared with the other first-degree relatives. Again the results were very satisfactorily consistent. As further tests of consistency it is important to compare data from second- and, if possible, third-degree relatives with data from first-degree relatives. Also, it would be very informative to discover the incidence in people related to the propositi by marriage only, such as brothers-in-law and sisters-in-law. These comparisons, and particularly that of the 'in-law' relatives, should show whether the correlations estimated are seriously inflated by environmental similarity, which is one of the major criticisms of the validity of heritabilities estimated from human data.

Sex difference

Three of the diseases analysed in the previous paper had different incidences in males and females, and the analyses were made with the assumption that the heritability was the same in the two sexes. This assumption is not necessary, and it is possible to examine the results more closely for consistency. The test of consistency is made by equation (2) of the present paper. Four regressions of relatives on propositi are available: male on male, female on female, female on male, and male on female. The first two, from like-sexed relatives, provide estimates of the heritability in males and females respectively (h_m^2 and h_f^2); the last two, from unlike-sexed relatives, both provide estimates of $h_m h_f r_G$, by equation (2), where r_G is the genetic correlation expressing the extent to which liability in males and females is influenced by the same genes. Table 6 shows the values obtained for peptic ulcer, congenital pyloric stenosis and club-foot. The test of consistency can be made by computing $h_m h_f$ from the separate heritabilities esti-

mated from the like-sexed relatives, and comparing this with $h_m h_f r_G$ estimated from the unlike-sexed relatives; the ratio of the second to the first is an estimate of r_G. It is very unlikely that the genetic correlation between the sexes is much below unity. Consistency will therefore be shown if the estimate of r_G is 1·0 or a little less. The estimates of r_G obtained from the three diseases are 1·0 for peptic ulcer, 1·2 for pyloric stenosis, and 1·3 for club-foot. With peptic ulcer the consistency is perfect; with the other two the regression coefficients from unlike-sexed relatives are rather higher than they should be in comparison with those from like-sexed relatives. In view of the standard errors of these regressions, however, the consistency is satisfactory.

Diabetes

The two major alternative hypotheses that have been proposed for the mode of inheritance of diabetes mellitus are a single gene and multifactorial inheritance. The single-gene hypothesis is clearly untenable in a simple form because the expected Mendelian ratios are not found. If there is a single gene responsible for what is often referred to as 'the diabetic genotype', then this gene must have a much reduced penetrance, and 75% or more of individuals with the 'diabetic genotype' are not diagnosed diabetics. To discriminate critically between a single gene with incomplete penetrance and multifactorial inheritance is unfortunately very difficult in the absence of planned test-matings. Barrai & Cann (1965), for example, in a study of Simpson's (1962) data on juvenile diabetics, conclude that the familial incidences are consistent with both hypotheses.

The single-gene hypothesis has been further modified by the supposition that there are minor, or modifying, genes at loci different from the major gene, which influence whether a person with the 'diabetic genotype' becomes diabetic or not. When modifying genes have to be introduced, the distinction between the two hypotheses themselves, as well as between their consequences, becomes very tenuous, as Edwards (1960) has pointed out. For example, Lamy, Frézal and Rey (1961) concluded that 'if enough of these secondary genes were present diabetes may occur, even in the absence of the major gene' (quoted from Steinberg, 1965). In this form the single-gene hypothesis is identical with the multifactorial hypothesis.

Thus the conflict—if there still is a conflict—is no longer between the hypotheses themselves but rather between the questions they lead the investigator to ask. Adherents to the single-gene hypothesis want to know if the gene is dominant or recessive, how frequently it leads to diabetes in those possessing it (i.e. its penetrance), whether the same gene is responsible for the diabetes in different families, what is the frequency of the gene or genes in the population, and what are the factors that determine whether the 'diabetic genotype' is expressed as overt diabetes or not. Adherents to the multifactorial hypothesis think that it is impossible at the moment to answer these questions because the individual genes cannot yet be unambiguously identified. The genetic properties that can be investigated are therefore the combined properties of all the genes in aggregate. The concept of the 'diabetic genotype' is replaced by that of liability, and the questions to be asked concern the causes of variation of liability. This approach can lead to a better understanding of the disease, but it is not a substitute for the study of the individual genes. Eventually it will be possible by biochemical means to identify some, at least, of the genes responsible for diabetes: the discovery of a biochemically different insulin in juvenile diabetics (Roy, Elliot, Shapcott & O'Brien, 1966) is an encouraging beginning. If this difference proves to be inherited as a single gene, as it seems likely to be, then one of the genes causing early-onset

diabetes will have been identified. If one of the genes concerned is eventually identified and can be studied the question will arise of how 'important' this gene is in the aetiology of diabetes. Here the concept of liability and its variance will be needed, because the 'importance' of a gene will have to be assessed from its effect on liability and from the amount that it contributes to the variance of liability in the population.

SUMMARY

The method of analysing familial incidences to yield an estimate of the heritability of liability to a disease (Falconer, 1965) is developed more adequately for diseases with variable age of onset, and is applied to published data on diabetes mellitus.

The increase of incidence associated with a variable age of onset can be due to either an increase of the mean liability or an increase of the variance of liability. Consideration of the changes of liability that individuals may undergo as they grow older shows that an increase of variance with increasing age is to be expected; and, since the additional variance is likely to be mainly environmental, a reduction of the heritability is to be expected.

The method of analysis provides a valid estimate of the correlation of liability between relatives, even if the relatives differ in variance from the population from which the propositi were drawn. If the relatives and propositi differ in age, the heritabilities at the two ages may differ and the correlation then provides an estimate of $h_1 h_2 r_G$, where h_1 and h_2 are the square roots of the heritabilities at the two ages, and r_G is the genetic correlation between liability at the two ages. Estimation of the genetic correlation allows an assessment to be made of the extent to which the disease is genetically different in early- and late-onset cases.

The heritability of liability to diabetes, estimated from the sib correlation, decreases with increasing age. In people under 10 it is about 70 or 80 %, and it drops to about 30 or 40 % in people aged 50 and over. The decrease of the heritability is attributable to an increase of environmentally caused variation. The increased environmental variation is not enough to account in full for the increasing incidence, and so there is probably also an increase of the mean liability with increasing age. An increase of both the mean and the variance of liability is consistent with observed changes of glucose tolerance tests.

The overall heritability, with age disregarded, is about 35 %. Sibs, parents, and children with one or with two diabetic parents all gave consistent estimates of the overall heritability. Sibs may be a little more alike for environmental reasons than parents and children; they may be much more alike in early life, but the evidence on this was inconclusive.

Cases with early onset seem to be genetically different from cases with late onset, to the extent that the genetic correlation between liability at the approximate ages of 20 and 50 is probably less than 0·5.

The Discussion considers the evidence needed to establish the general validity of the method of analysis, and comments on the distinction between the single-gene and the multifactorial hypotheses for the inheritance of diabetes mellitus.

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