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The inheritance of liability to certain diseases, estimated from the incidence among relatives

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INTRODUCTION

It is now commonly recognized that many diseases that are not inherited in a simple manner have, nevertheless, some hereditary basis. The evidence that heredity plays some part comes from the observation that the incidence of the disease is higher among the relatives of affected individuals than it is in the general population. An increased incidence among relatives does not, however, go far toward providing an answer to the important question of how strong the hereditary factor is, because the difference of incidence has no simple genetic interpretation. The relative importance of heredity and environment in such a case is clearly a problem of quantitative genetics. The usual methods of quantitative genetics, however, are not immediately applicable because these are based on correlations between relatives in respect of some 'graded' character measurable on a continuous scale. Data in the form of incidences refer, in contrast, to an 'all-or-none' classification; individuals either have the disease or they do not. Though the affected individuals may sometimes be graded according to the degree of severity of their symptoms, the normal individuals, who are the majority, cannot be graded by the degree of their normality. The purpose of this paper is to suggest that the method developed in quantitative genetics for dealing with 'threshold characters' is applicable to data on the incidence of diseases, and that by its use we can get further towards an answer to the question of the relative importance of heredity and environment. (A fuller account of the method as applied in quantitative genetics will be found in Falconer, 1960.)

The question of most general interest about the genetic causation of a disease that is not simply inherited is probably the relative importance of heredity as a causative agent. This question is meaningful only when stated in terms of amounts of variation; i.e. the variation between individuals that causes some to be affected and some not. What fraction of this variation is attributable to genetic differences between individuals? This fraction may be called the 'degree of genetic determination'. Unfortunately the degree of genetic determination cannot be estimated from human data, unless possibly by the use of twins, but a related quantity, the 'heritability', can be estimated. The distinction between the degree of genetic determination and the heritability is as follows. Two kinds of genetic variation have to be distinguished, 'additive' and 'non-additive'. The additive genetic variance is attributable to the average effects of genes considered singly, as transmitted in the gametes. The non-additive genetic variance is attributable to the additional effects of these genes when combined in diploid genotypes. It therefore arises from dominance and interaction between genes at different loci; if there is no dominance or interaction there can be no non-additive variance. The degree of genetic determination is the total genetic variance (additive + non-additive) as a proportion of the total phenotypic variance (genetic + non-genetic). The heritability is the additive genetic

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variance alone as a proportion of the phenotypic variance. The heritability expresses the extent to which the phenotypes exhibited by parents are transmitted to their offspring. It therefore determines the magnitude of the correlation between relatives. Though of less general interest than the degree of genetic determination, it it is of more practical use for predictive purposes, for example, in genetic counselling. The degree of genetic determination may be equal to the heritability (i.e. in the absence of dominance or interaction) or it may be greater, but it can never be less.

The heritability is estimated from the degree of resemblance between relatives, expressed as a correlation or regression coefficient. The method proposed in this paper for dealing with diseases is primarily a device for converting the information contained in the incidences into an estimate of the correlation between relatives. The genetic interpretation of the correlation, from which the heritability is estimated, is subject to the same sources of error as with continuously varying characters. These possible sources of error, which are already well known, are not considered in the main part of the paper but are mentioned in the Discussion. The first part of the paper presents the theory of how the heritability can be estimated from data in the form of incidences. The Theory section refers to data in the simplest form, consisting of two observed incidences, that in the general population and that in relatives of affected individuals, and then deals with some refinements necessary for analysing more complicated data. Then follows a section on 'Applications' in which the method is applied to published data on four diseases. This section illustrates in detail how the formulae developed in the Theory section are used.

THEORY

'Liability' and the 'threshold'

To overcome the difficulty of the all-or-none character of a disease we have to suppose that there is in fact an underlying gradation of some attribute immediately related to the causation of the disease. If we could measure this attribute, it would give us a graded scale of the degree of affectedness or of normality, and we should find that all individuals above a certain value exhibited the disease and all below it did not. This hypothetical graded attribute will be referred to here as the individual's 'liability' to the disease. The term susceptibility is not suitable because it implies the innate tendencies as distinct from the external circumstances. The term liability is intended to express not only the individual's innate tendency to develop or contract the disease, i.e. his susceptibility in the usual sense, but also the whole combination of external circumstances that makes him more or less likely to develop the disease. For example, in the case of an infectious disease the individual's susceptibility in the usual sense depends on his immunological defences, but the liability includes also the degree of exposure to the infective agent. The point on the scale of liability above which all individuals are affected and below which all are normal will be called the 'threshold'. The variation of liability, the threshold, and the resulting incidence are illustrated in Fig. 1. The concepts of an underlying variable, here called the liability, and the threshold were proposed by Carter (1961, 1963) in connexion with congenital pyloric stenosis. The concepts can be developed quantitatively so that the correlation between relatives in respect of liability can be estimated from data consisting of incidences.

For the quantitative development of the idea it is necessary to define the variation of liability as being normally distributed. This gives a unit for the expression of the degree of liability, the

unit being the standard deviation. This definition of the liability as being normally distributed does not make an unwarranted assumption about the real nature of the liability: it simply specifies that in order to express the degree of liability we shall choose a scale of measurement which, if we could measure the liability, would yield a normal distribution. It does, however, exclude situations where the variation of liability is discontinuous, which would apply to diseases determined by a single major gene. The method of analysis to be developed therefore applies only to diseases whose genetic component is multifactorial, or if there are few genes, where these have effects that are small in relation to the non-genetic variation.

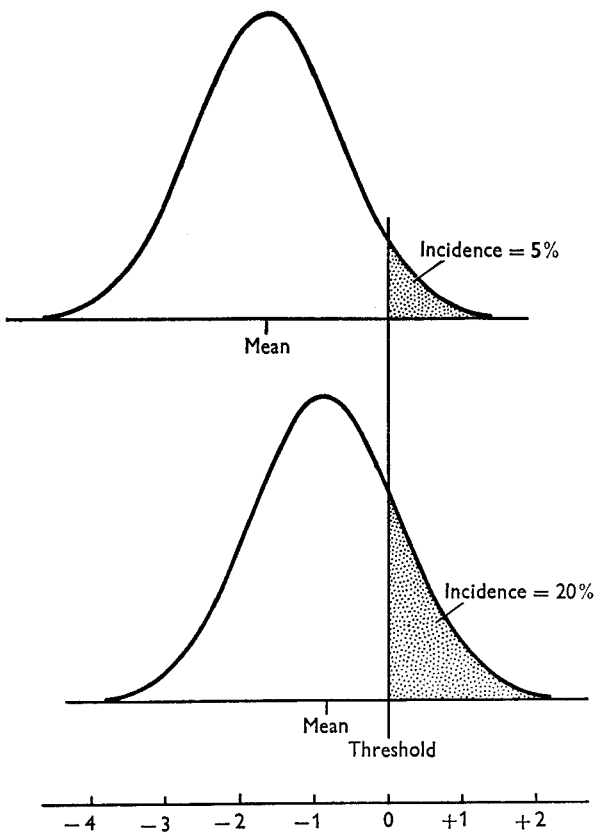

Fig. 1. Illustrations of two populations or groups with different mean liabilities. The liability is normally distributed, with the same variance in the two groups. The groups are compared by reference to a fixed threshold. The stippled portions are the affected individuals with the incidences shown.

The definition of the threshold, as the point on the scale of liability above which all individuals are affected and below which none are affected provides a fixed point by which to compare different populations or groups with different incidences. Fig. 1 illustrates the comparison of two populations on the basis of a fixed threshold. The lower distribution in the figure, with an incidence of 20 %, has a higher mean liability than the upper distribution with an incidence of 5 %. The two distributions illustrate the way in which data in the form of incidences are to be interpreted in terms of the liability and the threshold, though the incidences shown are much higher than are found for most diseases. The upper distribution represents the general popula-

tion, and the lower distribution, with a higher incidence and higher mean liability, represents the relatives of affected individuals. For the genetic analysis of data in this form we need to evaluate the difference in mean liability between the two distributions, and we need to know also the mean liability of the affected individuals themselves, whose relatives appear in the lower distribution. These mean liabilities can be evaluated as follows.

Evaluation of mean liabilities. If the mean liabilities of two groups are to be compared and the difference of liability evaluated, one important assumption has to be made. It is that the variance of liability is the same in the two groups. This assumption is unavoidable because without it there is no common scale on which the liabilities of the groups can be compared. The unit of measurement on the common scale is the standard deviation of the distribution, and this scale is shown at the foot of Fig. 1 with standard deviations marked off from the threshold as zero. On this scale the mean liability of the upper distribution is $-1{\cdot}6\,\sigma$, i.e. 1·6 standard deviations below the threshold, and that of the lower distribution is $-0{\cdot}8\,\sigma$.

The evaluation of the mean liability of the population is made by reference to tables of the normal distribution. With a given incidence, q, a table of the normal deviate x (single-tailed) gives the deviation, x, in standard deviation units, of the threshold from the mean. These tables are provided by Pearson (1931), Kelley (1947), Comrie (1949), Pearson & Hartley (1962). (Of these, only Comrie's tables cover incidences below 0·1 %.) A table suitable for the present problem is reproduced here in Appendix A.

Fig. 2 shows the same two normal distributions as Fig. 1, but with the values to be obtained from the tables, or Appendix A, entered on them. The upper distribution represents the general population with an incidence, q_g. The corresponding deviation of the threshold from the mean is x_g. This is given as a positive value in the tables, so the mean liability, G, of the population is x_g units below the threshold, T, or $-x_g$ units if liability is measured from the threshold as zero. Some care is thus needed with the signs in converting the values entered in the tables into mean liabilities. The lower distribution in Fig. 2 represents the relatives of affected individuals with an incidence q_r. The corresponding mean liability, R, is x_r units below the threshold. Reference to Fig. 2 will show that the difference of mean liability between the relatives and the general population is $R-G = x_g-x_r$.

The mean liability of the affected individuals in the general population is marked A in Fig. 2. This deviates from the mean of the population as a whole by the amount a in standard deviation units. The value of a depends on the incidence and can be obtained from tables of the normal distribution or from Appendix A. Not all the tables cited above give a itself, but it can be obtained as $a = z/q$, where z is the height of the ordinate of the normal curve at the threshold corresponding to the incidence, q. The values of a given in the tables and Appendix A are, like x, positive deviations from the population mean. Reference to Fig. 2 will show that the mean liability, A, of the affected individuals as a deviation from the threshold is given by $a-x$ and is positive.

For the analysis of some data, as will be explained later, it is necessary to know also the mean liability of the normal individuals in the general population. This obviously deviates very little from the mean of the population as a whole unless the incidence is very high. The deviation is shown as n in Fig. 2. It is not necessary to have n tabulated because it is related to a in the following way. As $a = z/q$, so $n = z/p$ where $p = 1-q$. Therefore $n = aq/p$.

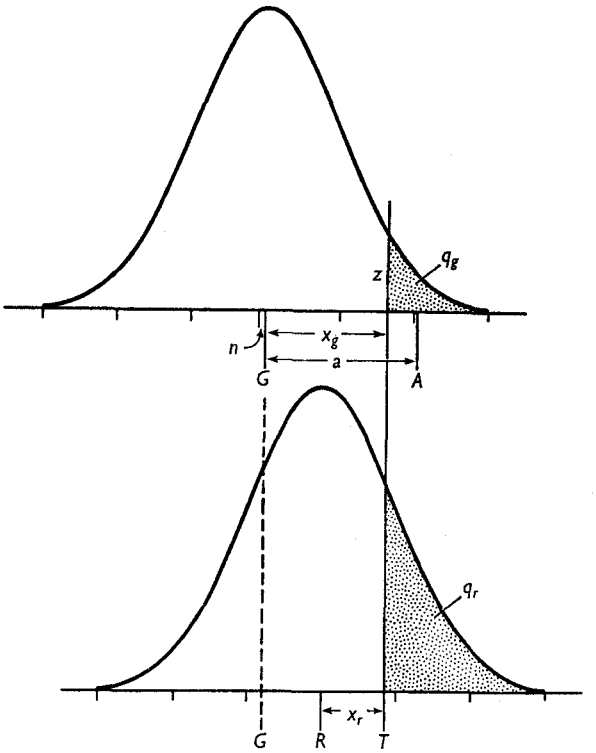

Fig. 2. Two distributions representing the general population above, and the relatives of affected individuals below, compared with reference to the fixed threshold, T.

G = mean liability of general population,
A = mean liability of affected individuals in the general population,
R = mean liability of relatives,
q = incidence, i.e. proportion of individuals with liabilities exceeding the threshold,
x = deviation of threshold from mean, i.e. the normal deviate,
z = height of the ordinate at the threshold,
a = mean deviation of affected individuals from the population mean ($= z/q$),
n = mean deviation of normal individuals from the population mean ($= z/(1-q)$),
subscript g refers to the general population, subscript r to the relatives.

GENETICS

Regression of relatives on propositi. Data in the form of two incidences, leading to the evaluation of the two mean liabilities illustrated in Fig. 2, will be recognized by those familiar with quantitative genetics as analogous to a 'selection experiment'. The affected individuals, with mean A, are 'selected' out of the general population with mean G. The difference of mean, $A-G$, represents the 'selection differential'. The affected individuals are the propositi, or index patients, whose relatives are found to have a mean liability of R. The difference between the mean of the relatives and the mean of the general population, $R-G$, represents the 'response'. The ratio of these two differences of mean liability is the regression of relatives on propositi in respect of liability. The regression, b, is therefore given by

$$b = \frac{R-G}{A-G}. \tag{1}$$

Fig. 3 shows the meaning of this regression diagrammatically. The regression coefficient, b, is the slope of the line drawn through the origin G, and the point corresponding to the value R,

in the relatives and A in the propositi. Since the variances of liability are necessarily assumed to be the same in the relatives as in the general population, the regression in equation (1) is numerically the same as the correlation of liability between relatives of the sort under consideration.

The regression of relatives on propositi is expressed in equation (1) as the ratio of two differences of mean liability. The evaluation of these mean liabilities from the observed incidences by reference to tables of the normal distribution was explained in the previous section. When equation (1) is expressed in terms of the quantities to be obtained from the tables it becomes

$$b = \frac{x_g - x_r}{a}. \tag{2}$$

The table in Appendix A gives the values of x and a corresponding to incidences from 0·01 % upwards. To evaluate the regression, take x_g and a both corresponding to the incidence in the general population, and x_r corresponding to the incidence in the relatives, and enter these values in equation (2). The standard error of the estimate of the regression coefficient obtained in this way can be calculated from the formula given in Appendix B (Method 1). The derivation of the sampling variance is outlined in Appendix C.

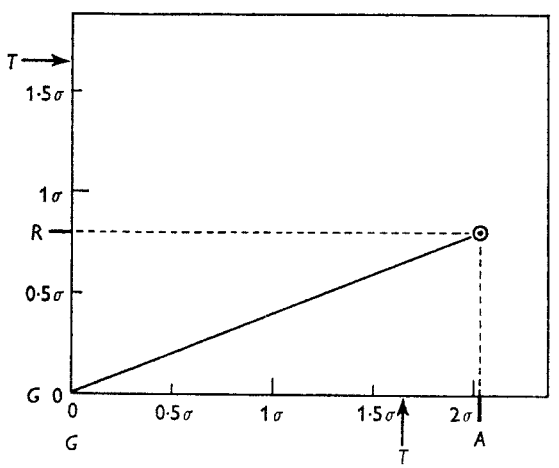

Fig. 3. Diagrammatic representation of the regression of relatives on propositi. The figure is drawn to scale for the values in Figs. 1 and 2. G = mean liability of general population; A = mean liability of affected individuals (propositi); R = mean liability of relatives of propositi. The axes are marked in standard deviation units, and the position of the threshold is marked by T. The regression coefficient is given by $b = (R-G)/(A-G)$.

Estimation of the heritability. The regression of relatives on propositi leads very simply to an estimate of the heritability of liability. This cannot be explained in detail here and the reader is referred to Falconer (1960) for a fuller explanation. The connexion between the regression of relatives on propositi and the heritability is briefly as follows. Let P be the phenotypic value (i.e. the liability) of any individual, R the phenotypic value of a relative, and r the coefficient of relationship. Then the regression of R on P is $b_{RP} = \mathrm{cov}_{RP}/V_P = rV_A/V_P = rh^2$, where cov_{RP} is the covariance, V_P is the phenotypic variance of individuals, V_A is the additive genetic variance, and h^2 is the heritability defined as the ratio of the additive genetic variance to the total phenotypic variance. Since the liability of individuals cannot be measured, the regression has to be derived from the mean liabilities of groups of individuals as in equation (1), where

A refers to a group of affected individuals and R to a group of their relatives. The covariance of an individual with the mean of any number of relatives of the same sort is, however, the same as with one relative. Therefore it does not matter how many relatives are contributed by each propositus, and the relationship between the regression in equation (1) and the heritability of liability is

$$b = rh^2.$$

The heritability is therefore estimated from the regression by

$$h^2 = b/r. \tag{3}$$

The coefficient of relationship, r, for first-degree relatives is $\frac{1}{2}$. Thus if the relatives are full sibs, parents, or children of the propositi, the heritability is estimated as

$$h^2 = 2b.$$

Other sorts of relatives that might be used are uncles and aunts, or nephews and nieces; with these $r = \frac{1}{4}$ and so $h^2 = 4b$. With first cousins (single) $r = \frac{1}{8}$ and $h^2 = 8b$. Twins present special problems and will be discussed separately. Any number of relatives of the same sort can be included and it does not matter if some propositi contribute more than others. When the relatives are brothers or sisters then, of course, the propositus must not be counted with his sibs in the incidence among relatives. If two members of the same sib family appear among the affected propositi then, provided the two propositi were ascertained independently, the family should be counted twice in the data on relatives, with one of the affected propositi included as an affected relative.

Data from twins present some special difficulties in the genetic interpretation, which are commented on in the Discussion. There is, however, no difficulty in using data from twins to estimate the regression of twin relatives on the co-twin propositi, which is equivalent to the twin-correlation in respect of liability. This would be done in exactly the same way as for any sort of relative. But it is important to note that the twin pairs must have been ascertained through one or both members being affected by the disease in question. (If both were affected and were ascertained independently the pair would be counted twice.) Thus the pairs will consist of one affected member, which is the propositus, and one affected or normal member which is the 'relative'. The incidence among the 'relatives' is the incidence required for the calculation. This incidence is the same as the proportion of concordant pairs, when ascertained in the manner stated. Identical and fraternal pairs must, of course, be analysed separately. If the regression is to be used to estimate the heritability, in spite of the difficulties in the genetic interpretation, the appropriate coefficient of relationship, r, is 1 for identical pairs and $\frac{1}{2}$ for fraternal pairs.

Fig. 4 provides a quick means of obtaining an approximate estimate of the heritability directly from the observed incidences, without any computation. The graphs, which are based on equations (2) and (3), with $r = \frac{1}{2}$, show the incidence in first-degree relatives of affected individuals plotted against the incidence in the general population, for different values of the heritability. The scales of incidence on the horizontal and the vertical axes are both logarithmic. To use the graphs, find the point corresponding to the observed incidence in the general population read along the horizontal axis and the observed incidence in the relatives of propositi read along the vertical axis. The sloping line to which this point lies nearest then gives the heritability to the nearest 10% and interpolation can be made if desired. The heritabilities

marked against the sloping lines in the figure are those obtained by doubling the regression of relatives on propositi. The heritabilities shown are therefore appropriate to data from first degree relatives.

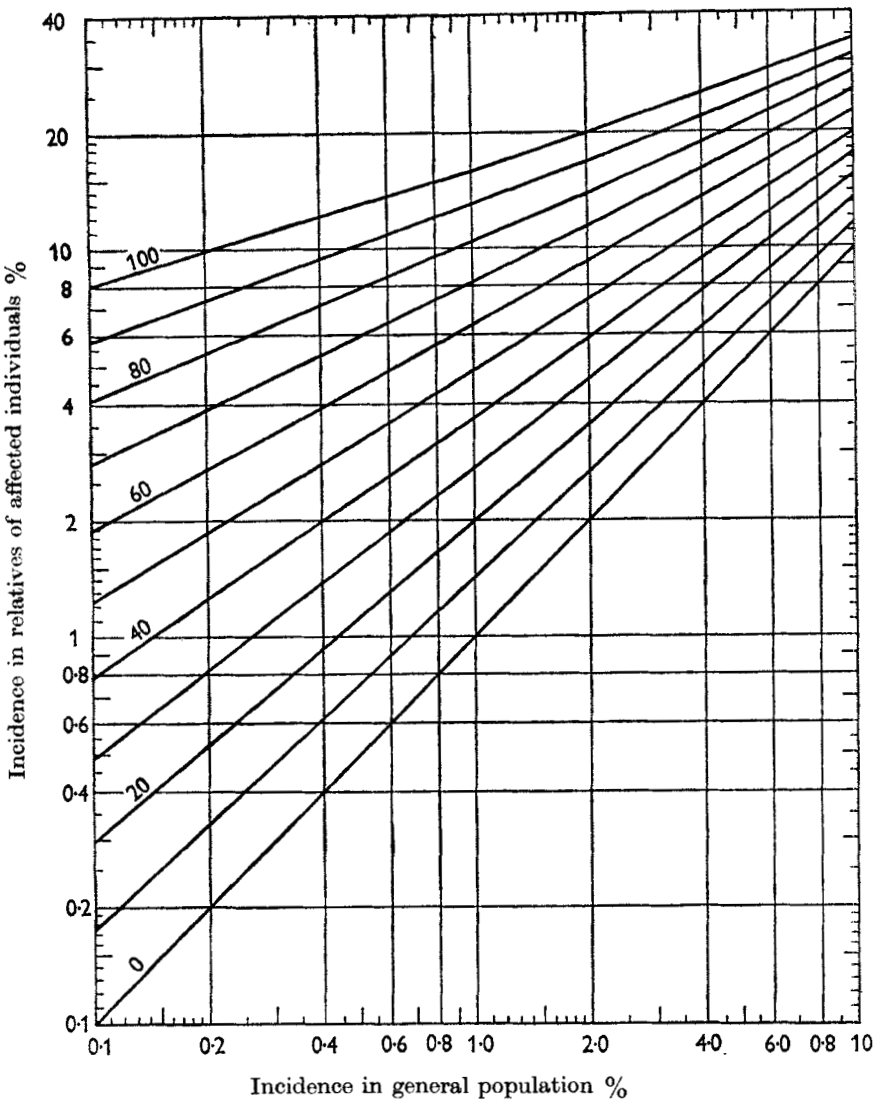

Fig. 4. Graph for estimating the heritability of liability from two observed incidences, when the relatives are sibs, parents, or children. Explanation in text.

Some refinements and complications

There are several complicating circumstances likely to be met with in the collection and analysis of data, which call for some minor modifications in the calculation of the regression of relatives on propositi. These do not affect the estimation of the heritability from the regression coefficient. The complications arise mainly from the fact that in the method described the incidence in the general population has been made to serve two purposes, and the incidence observed may not be suitable for both purposes. The incidence in the general population was used first to evaluate the mean liability of affected individuals. For this purpose, the general

population sampled should be representative of the population from which the affected individuals were drawn. Secondly, the mean liability of the general population, evaluated from the incidence, was compared with the mean liability of the relatives. For this purpose the sample of the general population should be representative of the population to which the relatives belong. This is particularly important because the whole procedure rests on the variance of liability being the same in the two groups compared. It is not always possible to obtain a single estimate of the incidence in the general population that satisfies the requirements of both purposes for which it is to be used. Some modifications of the procedure for calculating the regression of relatives on propositi are then needed. These are described in the sections that follow.

Data from controls. The best way to obtain a sample of the general population that is comparable with the relatives of affected individuals is from a series of 'controls'. This will probably also be the most convenient way to collect data on the general population if the incidence is not already known and has to be determined as part of the investigation. The control propositi are individuals not suffering from the disease in question, chosen for being the same as the affected propositi in sex, age, and any other characteristic that seems important. The control propositi are questioned about their relatives in the same way as the affected propositi are, and the incidence among the control relatives is taken as the estimate of the incidence in the general population. If the control propositi are well matched with the affected propositi, then the control relatives provide a good comparison with the relatives of affected individuals and, in particular, the assumption of equal variance of liability is less likely to be erroneous. For the purpose of comparison with the relatives, therefore, the incidence in the general population can be satisfactorily estimated from a control series.

The use of controls, however, introduces two small errors. Both are so small as to be hardly worth consideration, but they will be pointed out for the sake of completeness, especially as one can be easily removed. Both errors arise from the fact that the control relatives are not strictly representative of the population from which the affected propositi were drawn. Since the control propositi were selected for being unaffected by the disease, the relatives of the control propositi are expected to have a mean liability slightly below that of the general population in the strict sense. Consequently the relatives of affected propositi will differ more in mean liability from the relatives of control propositi than from the general population in the strict sense. In other words, the difference of mean liabilities in the numerator of the regression equation will be too great. This error can easily be overcome by taking account of the selection of the control propositi. Just as the affected propositi are selected out of the general population for having a high liability, so are the control propositi selected for having a low liability. The situation is illustrated by the upper distribution of Fig. 2, where the difference of mean liability between the control propositi and the general population is indicated by the deviation marked n. Whereas, before, the ratio giving the regression of relatives on propositi had a as denominator, now the appropriate denominator is $a+n$, because this is the total 'selection' that has given rise to the 'response' observed in the difference between the relatives of affected and of control propositi. The regression thus becomes

$$b = \frac{x_c - x_r}{a+n},$$

where x_c is the deviation of the threshold from the mean of the control relatives, evaluated from q_c, the incidence in the control relatives. It was stated earlier that n itself need not be evaluated

because it can be expressed as $n = aq/p$, where $p = 1-q$. When this is done, the formula for the regression, based on data from controls in place of the general population, simplifies to

$$b = \frac{p(x_c - x_r)}{a}. \tag{4}$$

The sampling variance of this estimate is given in Appendix B (Method 2). Since p will in most cases be very nearly 1, equation (4) differs little from equation (2). An approximate estimate of the heritability can therefore be obtained from Fig. 4, even though the incidence in the general population is estimated from control relatives.

The second error introduced by the use of controls arises from the fact that the incidence among the control relatives is not, strictly speaking, suitable for evaluating the mean liability of the affected propositi, or of the control propositi, which should be evaluated from the incidence in the general population from which the propositi were drawn. The error consequently introduced in the evaluation of a and p in equation (4) is not easily overcome by adjustment of the formula, but it is so small that it can be safely neglected. It would, of course, be possible to estimate the incidence in the general population in the strict sense as well as that in the control relatives, and to use this for the evaluation of a and p. Three observed incidences would then be used. The additional sampling errors introduced would, however, greatly outweigh the improved theoretical accuracy. There are, nevertheless, circumstances under which three incidences are required, and these will now be discussed.

Incidence differing in the two sexes. If the incidence of a disease differs in the two sexes this leads to a difference of incidence among the relatives of affected males and affected females which may at first sight seem puzzling. The analysis by means of the regression coefficients, however, provides an explanation of the differing incidences, and the differing incidences, in turn, offer an interesting means of testing the validity of the analysis. Carter (1961, 1963) showed how the higher incidence of congenital pyloric stenosis among the relatives of affected females than among those of affected males could be explained on the basis of an underlying variable and a threshold. Fig. 1 will serve to illustrate the interpretation in terms of liability, the upper distribution representing females and the lower one males. The incidence in the general population is lower in females than in males. With liability defined as being measured from a fixed threshold, females have a lower mean liability than males. Consequently affected females deviate more from the mean of their sex than do affected males. If the liability is to any extent inherited, this will result in the relatives of affected females having a higher mean liability than those of affected males.

To obtain a meaningful estimate of the heritability from the regression of relatives on propositi, it is necessary to separate the sexes and determine the mean liability in each sex of propositi and each sex of relatives. Regressions can then be calculated as follows. It is obviously possible to analyse each sex separately, by the methods already described, and so to obtain two estimates of the heritability, one for males and one for females. These two estimates need not necessarily be the same, because the sexes may differ in the variance of liability arising from environmental causes. The two estimates for the sexes separately make use of only the 'like-sexed' relatives, i.e. male relatives of affected males and female relatives of affected females. The regression of relatives on propositi can, however, be calculated for the 'unlike-sexed' relatives —female relatives of affected males and male relatives of affected females—provided the inci-

dences are taken from the appropriate sexes. This clearly calls for the use of three incidences because the propositi of one sex and the relatives of the other belong to different general populations with different mean liabilities, and possibly with different variances. For the calculation of the regression of relatives on propositi two different general population means are required, and equation (1) becomes

$$b = \frac{R - G_R}{A - G_A},$$

where G_R is the mean of the general population of the same sex as the relatives and G_A is the mean of the general population of the same sex as the affected propositi. In terms of the quantities obtained from the tables, the regression based on three incidences is

$$b = \frac{x_{gr} - x_r}{a_g}, \tag{5}$$

where x_{gr} is evaluated from the incidence in the general population comparable with the relatives, and a_g is evaluated from the incidence in the general population comparable with the propositi. The standard error of the regression estimated in this way is given in Appendix B (Method 3).

The best sample of the general population for comparison with the relatives will be from a control series, as explained in the previous section. The control relatives must, of course, be of the same sex as the relatives of affected propositi. A similar modification of the formula is then called for and the regression is obtained as

$$b = \frac{p_g(x_c - x_r)}{a_g}, \tag{6}$$

where a_g and p_g are evaluated from the incidence in the general population comparable with the propositi, and x_c from the incidence in the control relatives. The sampling variance is given in Appendix B (Method 4).

The regression of relatives of one sex on propositi of the other, calculated in the manner outlined, is quite valid, even if the variances are different. The relationship of this regression to the heritability of liability is, however, not quite straightforward for the following reasons. The resemblance in liability between relatives of one sex with affected individuals of the other depends not only on the heritabilities in both sexes but also on the extent to which the genetic component of liability is dependent on the same genes in the two sexes. It is possible that some genes affect the liability in one sex but not in the other. The extent to which liability in the two sexes depends on the same genes is expressed as the genetic correlation, r_G, between the sexes in respect of liability. Application of the theory of genetic correlation (see Falconer, 1960 for details) to the problem under discussion shows that if the regression coefficient is multiplied by two (or by the appropriate factor) this gives an estimate of $h_m h_f r_G$, where h_m and h_f are the square roots of the heritabilities in males and females, respectively. In principle, therefore, the genetic correlation between liability in the two sexes can be estimated, but an estimate precise enough to be meaningful would probably require data on a very large scale.

Four separate regressions can be calculated, two from like-sexed and two from unlike-sexed relatives. When multiplied by the appropriate factor for the coefficient of relationship, the first two estimate h_m^2 and h_f^2, respectively, and the second two both estimate $h_m h_f r_G$. Thus the two estimates from unlike-sexed relatives should be the same, even if the heritabilities in males and

females are different. If all four estimates are the same, then the genetic correlation must be unity, within the limits of sampling error. The three examples given later in this paper, in which the incidence differs in males and females, all show fairly close agreement between the four estimates of the heritability. These cases, therefore, give no evidence of different heritabilities *in* males and females, or of the liabilities in males and females being influenced by different genes.

If the four separate estimates of the heritability do not differ significantly, they can be combined into a single estimate by taking a weighted mean, the weight given to each being the reciprocal of its sampling variance. The sampling variance of this combined estimate is given approximately by the reciprocal of the sum of the weights. This is only approximate because the sampling variances of the separate estimates are not uncorrelated.

Incidence changing with time. Another situation in which three incidences might be required for the calculation of the regression is when the incidence of the disease is known to be changing with time. If the propositi and their relatives belong to different generations, e.g. the relatives are parents or children, the propositi and relatives will belong to different general populations, with different incidences. The regression of relatives on propositi could be calculated by equation (5) or (6), but this procedure is not to be recommended for the following reasons. A time-trend in the incidence of a disease may be due either to a change in the mean liability or to a change in the variance of liability, and there is no means of knowing which is the cause. If it is only the mean that is changing, the estimate of the heritability from propositi and relatives in different generations would be valid. But if the variance is changing an essential assumption on which the calculation is based would be violated, and the estimate of the heritability would be invalid. The use of contemporaneous relatives, however, will yield an estimate of the heritability that is valid for the time at which the data are collected.

Incidence changing with age. Variation in the age of onset leads to an age-dependent incidence, the incidence increasing with age. The increase of incidence might be due to either an increasing liability or an increasing variance of liability. The consequences of an increasing variance will not be considered, and it will be assumed that the variance is the same in all age groups. With this assumption it is possible to compare the liabilities of different age groups. If the incidences are known for different age groups, the liabilities can be determined from the incidences, and the relationship between liability and age can thus be determined.

On the assumption that the liability and not the variance changes with age, the comparisons on which the estimation of the heritability is based are valid, provided the groups compared have the same age distributions. Some adjustment, or correction, for age differences may, however, be needed. The propositi, being affected, will tend to be above the average age, and therefore their relatives will also tend to be above the general population in average age. If this is so, the incidence in the general population, from which x_g in equation (2) is evaluated, should be adjusted so that it is the incidence expected in a general population with the age distribution as found in the relatives of the propositi. If the incidence in the general population were estimated from the relatives of control individuals, little or no adjustment would be needed, provided the controls were matched for age with the affected propositi. This would seem to be a situation in which control relatives would be particularly advantageous.

The incidence in the general population is also needed for the evaluation of a, the mean deviation of affected individuals. This incidence should not be adjusted to correspond with the

age distribution of the propositi, because the greater age of the propositi is one aspect of their higher liability which makes them affected, and any adjustment would remove some of the variation of liability whose inheritance is being evaluated. The incidence used to evaluate a should be that of the whole population from which the propositi were drawn.

If liability changes with age, some of the variation of liability is associated with the variation of age in the population or sample. In other words, age represents one of the non-genetic sources of variation of liability. The procedure outline for estimating the heritability retains this variation associated with age as part of the non-genetic variation. The proportionate amount of the variation that is associated with age may be of interest, and can be estimated as follows. If the population is divided into age groups, the mean liability of each group can be evaluated from the incidence in it. The variance of these mean liabilities, each mean being weighted by the number of individuals in the group, is then an estimate of the variance of liability associated with the variation of age in the population. Let this variance of liability between age groups be v. The variance within the age groups is 1, by definition. (The liabilities are evaluated in terms of unit variance.) Therefore the total variance of liability is $1+v$, and the proportion of the total that is associated with age is $v/(1+v)$.

APPLICATION

The following four examples will illustrate the application of the method. In the first two the computations are shown in some detail, but in the last two only the data and the results are given. In all but the fourth example data from different sorts of relatives have been combined because, though given separately, the data are insufficient to warrant making separate estimates of the heritability. The relatives combined are, of course, all of the same degree, and in no case were the separate estimates of the regression coefficients significantly different from one another.

The symbols used have the following meanings:

A = observed number of affected individuals in the sample,
N = total number of individuals in the sample,
q = incidence = A/N,
p = $1-q$,
x and a are the values corresponding to q, taken from the table in Appendix A, with linear interpolation,
b = regression coefficient of relatives on propositi,
V_b = sampling variance of b,
h^2 = heritability of liability to the disease in question.

1. *Renal stone disease* (*Calcareous calculi*) (McGeown, 1960). The data consist of the incidences in relatives of affected individuals (patients) and in relatives of unaffected controls matched for sex and age with the affected individuals. The sexes are not separated. The incidences in parents, sibs and offspring, each with their control series, are given separately but are here combined. The data and values needed for the computation are given in Table 1. The regression coefficient is calculated by equation (4) (Method 2 of Appendix B) as follows:

$$b = 0{\cdot}99593\ (2{\cdot}646-1{\cdot}959)/2{\cdot}960 = 0{\cdot}231.$$

Whence the heritability is

$$h^2 = 2b = 46\,\%.$$

The calculation of the standard error of the heritability is as follows. The first steps are not shown, but comparison of the first line with the formula in Appendix B (Method 2) will show what these steps are. The sampling variance of the regression coefficient is

$$\begin{aligned} V_b &= [0{\cdot}3365 - 0{\cdot}231\ (2{\cdot}948 - 2{\cdot}646)]^2 \times 0{\cdot}0189 + (0{\cdot}3365)^2 \times 0{\cdot}00496 \\ &= 0{\cdot}00134 + 0{\cdot}00056 \\ &= 0{\cdot}00190. \end{aligned}$$

The standard error of the heritability is given by

$$\text{S.E. } (h^2) = 2\sqrt{V_b} = 2 \times 0{\cdot}044 = 0{\cdot}09.$$

Thus the heritability of the liability to renal stone disease estimated from these data is

$$h^2 = 46 \pm 9\,\%.$$

It will be noted that by far the larger part of the sampling variance comes from the first term, arising from the sampling error of the incidence in the control relatives. This is because the sample of control relatives contains many fewer affected individuals than the sample of relatives of patients.

Table 1. *Renal stone disease*

Relatives of	A	N	q	p	x	a
Controls	6	1473	0·00407	0·99593	2·646	2·960
Patients	36	1437	0·02505	0·97495	1·959	2·337

2. *Congenital pyloric stenosis* (Carter, 1961). Here the incidence differs in males and females and so the sexes of both propositi and relatives must be treated separately to yield four estimates of the regression. Data are given for sibs and children of propositi, but these are here combined. The incidences in the general population are given, but without the numbers on which these are based. Therefore the standard errors cannot be exactly calculated and those shown are based on the assumption that the incidences in the general population are known without error. The solutions obtained are given with the necessary data in Table 2. The regression coefficients are obtained from equation (2) (Method 1 of Appendix B) for the like-sexed relatives, and from equation (5) (Method 3) for the unlike-sexed relatives.

Table 2. *Congenital pyloric stenosis*

General population		A	N	q %	x	a	b	$V_b \times 10^4$	$h^2 \pm$ S.E. %
Male		—	—	0·5	2·576	2·892	—	—	—
Female		—	—	0·1	3·090	3·367	—	—	—
Propositi	Relatives								
Male	Male	16	318	5·03	1·642	2·060	0·323	16·72	64 ± 8
Male	Female	7	326	2·15	2·024	2·394	0·369	29·16	74 ± 11
Female	Male	14	82	17·07	0·951	1·486	0·483	23·66	97 ± 10
Female	Female	5	76	6·58	1·508	1·945	0·470	43·57	94 ± 13
Weighted mean		—	—	—	—	—	0·397	6·27	79 ± 5

The calculations are as follows:

Propositi	Relatives	
Male	Male	$b = (2{\cdot}576 - 1{\cdot}642)/2{\cdot}892 = 0{\cdot}323$
Male	Female	$b = (3{\cdot}090 - 2{\cdot}024)/2{\cdot}892 = 0{\cdot}369$
Female	Male	$b = (2{\cdot}576 - 0{\cdot}951)/3{\cdot}367 = 0{\cdot}483$
Female	Female	$b = (3{\cdot}090 - 1{\cdot}508)/3{\cdot}367 = 0{\cdot}470$

The sampling variance of the first regression coefficient, to take just one as an example, is obtained as

$$V = \frac{1}{(2{\cdot}892)^2} \times \frac{0{\cdot}9497}{(2{\cdot}060)^2 \times 16} = 0{\cdot}001672.$$

The first terms in the formulae given in Appendix B are zero if the incidence in the general population is assumed to be estimated without error.

The four estimates of the regression coefficient have been combined by weighting each by the reciprocal of its sampling variance and taking a weighted mean. The sampling variance of this combined estimate is approximately the reciprocal of the sum of the weights. The combined estimate of the heritability, with its standard error, is $79 \pm 5\,\%$. The four separate estimates agree with each other reasonably well within the limits of their sampling errors.

3. *Club-foot* (*Talipes equino-varus*) (Wynne-Davies, 1964). As in the previous example, the incidence is different in males and females and the incidences in the general population are given without the numbers from which they are derived. Data from sibs and parents are given, but these are again combined here. The data and the solutions, obtained in the same manner as the previous example, are given in Table 3.

Table 3. *Club-foot*

General population		A	N	q %	x	a	b	$V_b \times 10^4$	$h^2 \pm$ S.E. (%)
Male		—	—	0·162	2·944	3·231	—	—	—
Female		—	—	0·080	3·156	3·429	—	—	—
Propositi	Relatives								
Male	Male	5	212	2·36	1·984	2·359	0·297	33·61	59 ± 12
Male	Female	0	187	0	—	—	—	—	—
Female	Male	5	80	6·25	1·534	1·968	0·411	41·17	82 ± 13
Female	Female	2	81	2·47	1·965	2·342	0·347	75·61	69 ± 17
Weighted mean		—	—	—	—	—	0·348	14·87	70 ± 8

One group of relatives contained no affected individual. With the incidence being lower in females than in males, this group—female relatives of affected males—is the one that would be expected to have the lowest incidence. The zero-incidence observed is not inconsistent with the estimates of the regression obtained from the other groups. The upper 95 % confidence limit for the number observed is 3·66 (from Fisher & Yates, 1943, Table $VIII_1$). This means that an observed number of 0 is not incompatible with an expectation of 3·66 out of 187, giving an incidence of 1·96 %. This incidence leads to $b = 0{\cdot}339$, $h^2 = 68\,\%$, which is not significantly different from the other estimates. The group with zero-incidence is necessarily excluded from the combined estimate of the heritability obtained from the weighted mean of the other three groups. This combined estimate of $h^2 = 70 \pm 8\,\%$ is therefore biased upwards.

4. *Peptic ulcer* (Doll & Buch, 1950). Peptic ulcer presents a complicated situation and its analysis certainly merits a more elaborate treatment than can be attempted here. There are two main complications—the composite nature of the disease and the age-dependent incidence. Doll & Kellock (1951) showed that the excess of incidence of peptic ulcers among relatives of propositi, as compared with the general population, was almost entirely due to ulcers at the same site—gastric or duodenal—as that of the propositus. From this they concluded that gastric and duodenal ulcers are genetically distinct entities. An analysis of the two combined, as

'peptic ulcer', will therefore yield an estimate that is an approximate average of the heritabilities of the two separate entities. Though the data given in the appendices to the two papers cited would probably allow the gastric and duodenal sites to be analysed separately, I have not attempted to do this.

Table 4. *Peptic ulcer. Incidence and mean liability* ($= -x$) *by age groups. Sampling variance of mean liability* $= pq/z^2N$

Males					Females				
Median age	N	q %	Mean liability	± S.E.	Median age	N	q %	Mean liability	± S.E.
20	499	0·80	−2·41	±0·18	—	—	—	—	—
30	1128	2·48	−1·96	±0·08	25	578	0·35	−2·70	±0·23
40	1375	4·58	−1·69	±0·06	40	236	0·85	−2·39	±0·26
50	1089	7·35	−1·45	±0·06	55	249	1·61	−2·14	±0·20
60	625	6·24	−1·54	±0·08	(65+)	17	11·76	−1·19	±0·40
(65+)	155	5·81	−1·57	±0·16	—	—	—	—	—

The data on peptic ulcer gives the incidence by age groups in a large sample of the general population, and the incidence increases with age in both sexes. Table 4 shows the incidences in each age group and the mean liabilities derived from them. Fig. 5 shows the mean liability plotted against age. In both sexes there is a regular linear increase of liability up to the age of about 50. The proportion of the total variance of liability that is associated with variation of age in the population is 8 % in both sexes, calculated in the manner described in the previous section. From this it can be inferred that the correlation between liability and age is about 0·3 (i.e. the square root of 0·08).

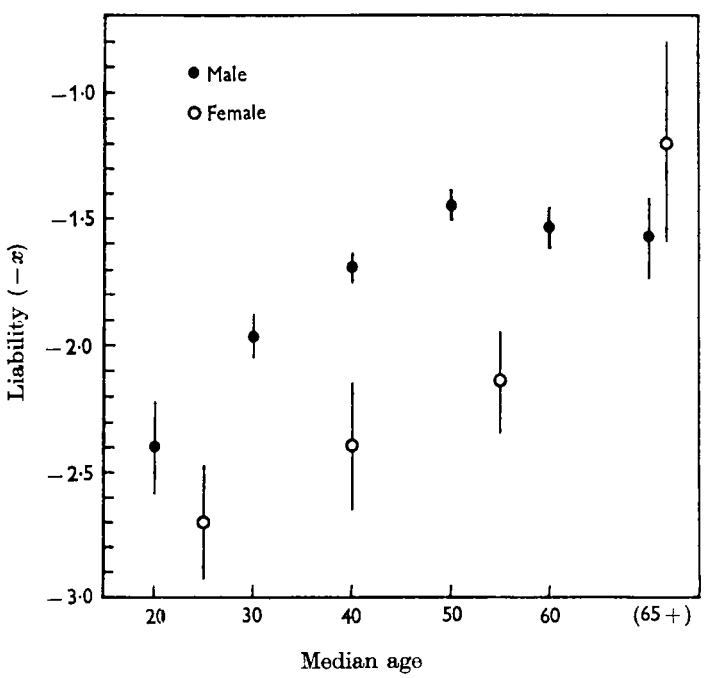

Fig. 5. Age effect on peptic ulcer. Mean liabilities of different age groups in the general population. The liability is expressed in standard deviations from the threshold. The vertical lines extend to ± one standard error of the estimated mean. Data from Doll & Buch (1950).

The data for the estimation of the heritability are the incidences in the general population and among the sibs of propositi. Since the incidence differs between males and females it is necessary to keep the sexes separate and obtain four estimates as in the previous examples. The sexes of propositi and their sibs were separated by reference to the appendix of Doll & Buch (1950), and the numbers so obtained were as shown in Table 5 here. The average age of the relatives of affected individuals was, as expected, above that of the general population. For comparison with the relatives, therefore, the incidence in the general population has to be adjusted to correspond with the age distribution among the relatives. For this purpose the age-corrected 'expectations' given by Doll & Buch have been used. It has been assumed that the age distribution among the relatives did not differ according to the sex of the propositi, which is probably not quite true because female propositi were older than male. Table 5 gives the values needed for the calculations, the values in brackets being those required only for the sampling variances. The four separate estimates of the heritability are satisfactorily consistent, and the combined estimate is $h^2 = 37 \pm 6\,\%$.

Table 5. *Peptic ulcer*

General population		A	N	q %	x	a	b	$V_b \times 10^4$	$h^2 \pm$ S.E. (%)
For comparison with:									
Propositi—male		223	4871	4·58	(1·687)	2·099	—		—
Propositi—female		10	1080	0·93	(2·353)	2·690	—	—	—
Relatives—male		Age corrected		5·39	1·608	(2·031)	—	—	—
Relatives—female		incidences		1·17	2·267	(2·612)	—	—	—
	Relatives								
Propositi	Relatives								
Male	Male	36	306	11·76	1·187	(1·677)	0·201	21·41	40 ± 9
Male	Female	9	318	2·83	1·906	(2·291)	0·172	78·46	34 ± 18
Female	Male	20	153	13·07	1·123	(1·624)	0·180	24·64	36 ± 10
Female	Female	5	165	3·03	1·876	(2·264)	0·145	66·56	29 ± 16
Weighted mean		—	—	—	—	—	0·183	8·70	37 ± 6

DISCUSSION

The usefulness of the method of analysis proposed in this paper is that it renders the observed incidences intelligible in terms of the heritability, and that a knowledge of the heritability can be of some predictive value. There are, however, some limitations in the method which may lead to error. The uses and limitations will be discussed in turn.

Interpretive value

The idea of an underlying variation of liability, and the analysis developed from it, provide a quantitative interpretation of the excess incidence of a disease among the relatives of affected individuals over the incidence in the general population. The incidences themselves, without further analysis, give a poor indication of the strength of hereditary factors because the incidences are not related in any simple way to the degree of inheritance, nor to the closeness of the relationship between the affected individuals and their relatives. A simple comparison of the incidence in relatives with the incidence in the general population will give a different picture according to whether the simple difference or the relative increase is taken as a measure of the importance of heredity. This can be seen from the graphs in Fig. 4. For example, diseases where

the heritability of liability was 50 % would give the following results, according to the incidence of the disease in the general population:

Incidence in general population (%)	Incidence in relatives (h^2 = 50 %) (%)	Difference of incidence (%)	Relative increase
0·1	1	0·9	10-fold
1	5	4	5-fold
10	20	10	2-fold

The diseases with different incidences in males and females that were analysed in the previous section provided examples of this situation. When the sexes were separated, the incidences among relatives seemed at first to be inconsistent, but were found on analysis to be all consistent with a single value of the heritability.

Predictive value

For predictive purposes it is the incidence itself in a specified group that is required, because the incidence expresses the probability that an individual of the group will have the disease. Knowledge of the heritability may, however, lead to a prediction which could not otherwise be made. The use of the heritability in this way may be made clearer by specific examples of genetic counselling. A patient suffering from renal stone disease may, for example, ask what is the chance that his children will suffer from the same disease. In this case, the incidence among first degree relatives is known (see Table 1 in the previous section), and nothing further is required: the probability is $2\frac{1}{2}$ % or 1 in 40. But if the required incidence were not known a useful prediction could still be made in the form of an upper limit, provided that the incidence in the general population were known. The upper limit would be obtained by assuming the heritability to be 100 %. Reference to Fig. 4 then shows that with a general population incidence of 0·4 %, the maximum incidence among first degree relatives is 12 %. As a more complicated example, suppose a woman says her sister had a club-footed son, and asks what is the chance of her having a club-footed child. The relationship in question is between single first cousins, and the required incidence is to be predicted from the known incidence among first degree relatives. The known incidence is used to estimate the heritability (h^2) which was found in example 3 of the previous section to be 70 %. The expected regression (b) for cousin relatives is $\frac{1}{8}h^2$, which in this case is 0·0875. To obtain the expected incidence among cousins of affected individuals we have to solve one of the regression equations for x_r. Because of the different incidences in the two sexes there will have to be different predictions for male and female children of the questioner. For male children equation (2) (Method 1 of Appendix B) is to be solved for x_r, with the value of b already found, and the values of x_g and a from the male general population (see Table 3 of the previous section). This gives

$$0{\cdot}0875 = \frac{2{\cdot}944 - x_r}{3{\cdot}231},$$

whence $x_r = 2{\cdot}661$. The incidence (q) corresponding to this value of x can now be found from Appendix A. It is 0·39 % or about 1 in 250. This is the probability that a male child will be club-footed. A similar calculation for female children can be made by solution of equation (5) (Method 3 of Appendix B). This gives

$$0{\cdot}0875 = \frac{3{\cdot}156 - x_r}{3{\cdot}231},$$

whence $x_r = 2{\cdot}873$, and the predicted incidence is 0·20 % or 1 in 500.

The above examples will show how a knowledge of the heritability might be used in genetic counselling. Prediction made in the same way would be helpful also in planning the collection of data on incidences, for deciding what size of sample should be collected. Since the standard error of the regression coefficient, and of the heritability estimated from it, depends chiefly on the number of affected individuals in the sample, it is important to have a sample large enough to include a reasonable number of affected individuals; if it includes none the sample is of very little use. Prediction of the incidence would be particularly helpful if it were planned to collect data from second or third degree relatives. The prediction may show that the size of sample required to be of any use would be impracticably large.

One other aspect of prediction deserves mention. If the heritability is found to be very high, the degree of genetic determination must also be very high and environmental factors, therefore, unimportant as causative agents of the disease. This does not mean, however, that curative or preventive measures will be ineffective. The environmental factors proved to be unimportant are those operating in the population sampled and these do not include special treatments or preventive measures. No prediction can be made from a knowledge of the degree of genetic determination about the efficacy of curative or preventive treatments. All that could be said in such a case is that one will have to look outside the range of normal environments experienced by the untreated population.

Sources of error

The method has two chief limitations from which error may arise: the assumption of a continuous distribution of liability, and the assumption of equal variances. The validity of the regression of relatives on propositi rests on these assumptions. Two other sources of possible error occur in the estimation of the heritability from the regression coefficient.

The requirement that the variation of liability should be continuous means that the method will break down if there is a major gene contributing to the causation of the disease. If the disease is simply inherited by a single dominant or recessive gene this will, of course, be known from family studies and the method would not be applied. A gene with incomplete penetrance, which did not give simple Mendelian ratios, might nevertheless cause a discontinuity in the distribution of liability. If the gene were recessive the situation would be detected by the estimate of the heritability from sibs being much higher than that from parents or children. If the gene were dominant the situation might be detected only by the estimated heritability being very obviously too high to be credited.

The requirement that the variance of liability should be the same in all groups being compared will probably not always be fulfilled, and the possibility of error from this source must be borne in mind. The error can be minimized by careful choice of the groups compared, as for example by the use of controls.

The estimation of the heritability from the regression of relatives on propositi is subject to two sources of possible error. The more important of these arises from non-genetic causes of resemblance between relatives. Members of the same family are obviously likely to be exposed to the same environmental factors associated with their diet, mode of life, exposure to infection, etc. Their liabilities to any particular disease will therefore tend to be correlated for purely environmental reasons, and the regression computed from the incidences may be in part, or even in whole, the consequence of these non-genetic causes of resemblance. The possibility must

therefore be recognized that the estimated heritability may be too high. This error seems likely to affect sibs more than other relatives.

The second source of error occurs only with estimates based on full sibs. It arises from the fact that non-additive genetic variance contributes to the correlation between full sibs and to the regression of full sib relatives on propositi. Doubling this regression coefficient gives an estimate of the additive genetic variance, together with one-half of the non-additive variance arising from dominance, as a proportion of the total. Therefore, if there is a significant amount of non-additive variance, the estimate obtained by doubling the regression coefficient of full sibs gives something in excess of the heritability but below the degree of genetic determination.

On account of the two sources of error discussed,the estimate of the heritability from full sibs may be somewhat higher than those from other sorts of relative. But if this is found, there is no means of knowing whether the discrepancy is due to environmental causes of resemblance or to non-additive genetic variance. It is obviously desirable that an estimate of the heritability should not be based on data from sibs alone. The inclusion of second or third degree relatives would be helpful for excluding error from environmental causes of resemblance.

In the examples analysed, the data from different sorts of relatives were not enough to be treated separately, so the absence of any obvious discrepancy does not exclude the possibility that the heritabilities may have been over-estimated. It is perhaps encouraging that the two congenital diseases showed higher heritabilities than the other two, and particularly that peptic ulcer, which might be expected to be the most seriously affected by non-genetic causes of resemblance, gave the lowest heritability.

Finally, the difficulties inherent in the use of twins, though they cannot be discussed in detail, must be mentioned. The difficulties arise from the same two sources of error that affect full sibs, but they are likely to be more serious. The first is that twins of both sorts may well resemble each other for environmental reasons even more than non-twin sibs. If this cause of resemblance could be excluded, the regression obtained from identical twin pairs would estimate the degree of genetic determination. If the environmental causes of resemblance can be assumed to be the same in their effects on fraternal as on identical pairs, then subtraction of the regression for fraternals from the regression for identicals will eliminate this source of error. What is left, i.e. what the difference between the two regression coefficients estimates, is one-half of the additive genetic variance plus three-quarters of non-additive variance arising from dominance, as a proportion of the total. If this is doubled it will over-estimate the degree of genetic determination. The conclusions that can be drawn from twins are therefore not very precise. If, however, a reliable estimate of the heritability has been obtained from other relatives, preferably parents or children, then the twin data can give a useful indication of the relative importance of non-additive genetic variance.

SUMMARY

1. Diseases that are not inherited in a simple manner by a single gene may have some degree of hereditary basis, which shows in a higher incidence among relatives of affected individuals than among the general population.

2. A method is presented by which the correlation between relatives can be derived from the known incidences. The method is based on the assumption of an underlying variable—called the liability—which expresses the combination of innate tendencies and external circumstances that make the individual more or less likely to develop the disease in question. Whether an

individual is affected or not depends on whether his liability exceeds or falls short of a fixed threshold.

3. The correlation of liability between relatives leads to an estimate of the heritability of liability, which estimates the relative importance of hereditary factors as causes of differences of liability between individuals.

4. Four examples from published data are analysed and the following estimates of the heritability (± standard error) obtained:

Renal stone disease	$46 \pm 9\%$
Congenital pyloric stenosis	$79 \pm 5\%$
Club-foot	$70 \pm 8\%$
Peptic ulcer	$37 \pm 6\%$

5. The method can be used to predict incidences not known by direct observation. The predictions could be useful in genetic counselling and in planning the collection of data.

I am greatly indebted to Dr B. Woolf for showing me how to work out the sampling variances and for advice on the preparation of Appendix A; and to Dr R. C. Roberts, Dr A. Robertson and Dr C. O. Carter for reading the manuscript and offering many valuable criticisms. I am grateful also to Dr C. A. Clarke, who first drew my attention to the problems discussed in this paper.

References

Carter, C. O. (1961). The inheritance of congenital pyloric stenosis. *Brit. Med. Bull.* **17**, 251.

Carter, C. O. (1963). The genetics of common malformations. *Second Internat. Conf. on Congenital Malformations*, p. 306.

Comrie, L. J. (1949). *Chamber's Six-Figure Mathematical Tables*, vol. 2. Edinburgh: Chambers.

Doll, R. & Buch, J. (1950). Hereditary factors in peptic ulcer. *Ann. Eugen., Lond.*, **15**, 135.

Doll, R. & Kellock, T. D. (1951). The separate inheritance of gastric and duodenal ulcers. *Ann. Eugen., Lond.*, **16**, 231.

Falconer, D. S. (1960). *Introduction to Quantitative Genetics*. Edinburgh: Oliver and Boyd.

Fisher, R. A. & Yates, F. (1943). *Statistical Tables*, 2nd ed. Edinburgh: Oliver and Boyd.

Kelley, T. L. (1947). *Fundamentals of Statistics*. Cambridge, Mass.: Harvard University Press.

McGeown, M. G. (1960). Heredity in renal stone disease. *Clin. Sci.* **19**, 465.

Pearson, K. (1931). *Tables for Statisticians and Biometricians*. Part 2. London: Biometrical Laboratory University College.

Pearson, E. S. & Hartley, H. O. (1962). *Biometrika Tables for Statisticians*, vol. 1. Cambridge University Press.

Wynne-Davies, R. (1964). Family studies and the cause of congenital club foot. *J. Bone Jt. Surg.* **46**B, 445.

APPENDIX A

Table of x and a for values of q from $q = 0{\cdot}01\,\%$ to $q = 50{\cdot}0\,\%$. q is the incidence; x is the normal deviate (single-tailed) exceeded by the proportion q; $a\ (= z/q)$ is the mean deviation of these individuals. Note changes of interval in q at $q = 2{\cdot}0\,\%$ and $q = 21{\cdot}0\,\%$. Compiled from Pearson (1931), Comrie (1949), and Fisher & Yates (1943).

q %	x	a	q %	x	a	q %	x	a	q %	x	a
			0·50	2·576	2·892	1·00	2·326	2·665	1·50	2·170	2·525
0·01	3·719	3·960	0·51	2·569	2·886	1·01	2·323	2·662	1·51	2·167	2·522
0·02	3·540	3·790	0·52	2·562	2·880	1·02	2·319	2·658	1·52	2·165	2·520
0·03	3·432	3·687	0·53	2·556	2·873	1·03	2·315	2·655	1·53	2·162	2·518
0·04	3·353	3·613	0·54	2·549	2·868	1·04	2·312	2·652	1·54	2·160	2·515
0·05	3·291	3·554	0·55	2·543	2·862	1·05	2·308	2·649	1·55	2·157	2·513
0·06	3·239	3·507	0·56	2·536	2·856	1·06	2·304	2·645	1·56	2·155	2·511
0·07	3·195	3·464	0·57	2·530	2·850	1·07	2·301	2·642	1·57	2·152	2·508
0·08	3·156	3·429	0·58	2·524	2·845	1·08	2·297	2·639	1·58	2·149	2·506
0·09	3·121	3·397	0·59	2·518	2·839	1·09	2·294	2·636	1·59	2·147	2·504
0·10	3·090	3·367	0·60	2·512	2·834	1·10	2·290	2·633	1·60	2·144	2·502
0·11	3·062	3·341	0·61	2·506	2·829	1·11	2·287	2·630	1·61	2·142	2·499
0·12	3·036	3·317	0·62	2·501	2·823	1·12	2·283	2·627	1·62	2·139	2·497
0·13	3·012	3·294	0·63	2·495	2·818	1·13	2·280	2·624	1·63	2·137	2·495
0·14	2·989	3·273	0·64	2·489	2·813	1·14	2·277	2·621	1·64	2·135	2·493
0·15	2·968	3·253	0·65	2·484	2·808	1·15	2·273	2·618	1·65	2·132	2·491
0·16	2·948	3·234	0·66	2·478	2·803	1·16	2·270	2·615	1·66	2·130	2·489
0·17	2·929	3·217	0·67	2·473	2·798	1·17	2·267	2·612	1·67	2·127	2·486
0·18	2·911	3·201	0·68	2·468	2·793	1·18	2·264	2·609	1·68	2·125	2·484
0·19	2·894	3·185	0·69	2·462	2·789	1·19	2·260	2·606	1·69	2·122	2·482
0·20	2·878	3·170	0·70	2·457	2·784	1·20	2·257	2·603	1·70	2·120	2·480
0·21	2·863	3·156	0·71	2·452	2·779	1·21	2·254	2·600	1·71	2·118	2·478
0·22	2·848	3·142	0·72	2·447	2·775	1·22	2·251	2·597	1·72	2·115	2·476
0·23	2·834	3·129	0·73	2·442	2·770	1·23	2·248	2·594	1·73	2·113	2·474
0·24	2·820	3·117	0·74	2·437	2·766	1·24	2·244	2·591	1·74	2·111	2·472
0·25	2·807	3·104	0·75	2·432	2·761	1·25	2·241	2·589	1·75	2·108	2·470
0·26	2·794	3·093	0·76	2·428	2·757	1·26	2·238	2·586	1·76	2·106	2·467
0·27	2·782	3·081	0·77	2·423	2·753	1·27	2·235	2·583	1·77	2·104	2·465
0·28	2·770	3·070	0·78	2·418	2·748	1·28	2·232	2·580	1·78	2·101	2·463
0·29	2·759	3·060	0·79	2·414	2·744	1·29	2·229	2·578	1·79	2·099	2·461
0·30	2·748	3·050	0·80	2·409	2·740	1·30	2·226	2·575	1·80	2·097	2·459
0·31	2·737	3·040	0·81	2·404	2·736	1·31	2·223	2·572	1·81	2·095	2·457
0·32	2·727	3·030	0·82	2·400	2·732	1·32	2·220	2·570	1·82	2·092	2·455
0·33	2·716	3·021	0·83	2·395	2·728	1·33	2·217	2·567	1·83	2·090	2·453
0·34	2·706	3·012	0·84	2·391	2·724	1·34	2·214	2·564	1·84	2·088	2·451
0·35	2·697	3·003	0·85	2·387	2·720	1·35	2·211	2·562	1·85	2·086	2·449
0·36	2·687	2·994	0·86	2·382	2·716	1·36	2·209	2·559	1·86	2·084	2·447
0·37	2·678	2·986	0·87	2·378	2·712	1·37	2·206	2·557	1·87	2·081	2·445
0·38	2·669	2·978	0·88	2·374	2·708	1·38	2·203	2·554	1·88	2·079	2·444
0·39	2·661	2·969	0·89	2·370	2·704	1·39	2·200	2·552	1·89	2·077	2·442
0·40	2·652	2·962	0·90	2·366	2·701	1·40	2·197	2·549	1·90	2·075	2·440
0·41	2·644	2·954	0·91	2·361	2·697	1·41	2·194	2·547	1·91	2·073	2·438
0·42	2·636	2·947	0·92	2·357	2·693	1·42	2·192	2·544	1·92	2·071	2·436
0·43	2·628	2·939	0·93	2·353	2·690	1·43	2·189	2·542	1·93	2·068	2·434
0·44	2·620	2·932	0·94	2·349	2·686	1·44	2·186	2·539	1·94	2·066	2·432
0·45	2·612	2·925	0·95	2·346	2·683	1·45	2·183	2·537	1·95	2·064	2·430
0·46	2·605	2·918	0·96	2·342	2·679	1·46	2·181	2·534	1·96	2·062	2·428
0·47	2·597	2·911	0·97	2·338	2·676	1·47	2·178	2·532	1·97	2·060	2·426
0·48	2·590	2·905	0·98	2·334	2·672	1·48	2·175	2·529	1·98	2·058	2·425
0·49	2·583	2·898	0·99	2·330	2·669	1·49	2·173	2·527	1·99	2·056	2·423
0·50	2·576	2·892	1·00	2·326	2·665	1·50	2·170	2·525	2·00	2·054	2·421

APPENDIX A (*cont.*)

q %	x	a	q %	x	a	q %	x	a	q %	x	a
2·0	2·054	2·421	7·0	1·476	1·918	12·0	1·175	1·667	17·0	0·954	1·489
2·1	2·034	2·403	7·1	1·468	1·912	12·1	1·170	1·663	17·1	0·950	1·485
2·2	2·014	2·386	7·2	1·461	1·906	12·2	1·165	1·659	17·2	0·946	1·482
2·3	1·995	2·369	7·3	1·454	1·899	12·3	1·160	1·655	17·3	0·942	1·479
2·4	1·977	2·353	7·4	1·447	1·893	12·4	1·155	1·651	17·4	0·938	1·476
2·5	1·960	2·338	7·5	1·440	1·887	12·5	1·150	1·647	17·5	0·935	1·473
2·6	1·943	2·323	7·6	1·433	1·881	12·6	1·146	1·643	17·6	0·931	1·470
2·7	1·927	2·309	7·7	1·426	1·876	12·7	1·141	1·639	17·7	0·927	1·467
2·8	1·911	2·295	7·8	1·419	1·870	12·8	1·136	1·635	17·8	0·923	1·464
2·9	1·896	2·281	7·9	1·412	1·864	12·9	1·131	1·631	17·9	0·919	1·461
3·0	1·881	2·268	8·0	1·405	1·858	13·0	1·126	1·627	18·0	0·915	1·458
3·1	1·866	2·255	8·1	1·398	1·853	13·1	1·122	1·623	18·1	0·912	1·455
3·2	1·852	2·243	8·2	1·392	1·847	13·2	1·117	1·620	18·2	0·908	1·452
3·3	1·838	2·231	8·3	1·385	1·842	13·3	1·112	1·616	18·3	0·904	1·449
3·4	1·825	2·219	8·4	1·379	1·836	13·4	1·108	1·612	18·4	0·900	1·446
3·5	1·812	2·208	8·5	1·372	1·831	13·5	1·103	1·608	18·5	0·896	1·443
3·6	1·799	2·197	8·6	1·366	1·825	13·6	1·098	1·605	18·6	0·893	1·440
3·7	1·787	2·186	8·7	1·359	1·820	13·7	1·094	1·601	18·7	0·889	1·437
3·8	1·774	2·175	8·8	1·353	1·815	13·8	1·089	1·597	18·8	0·885	1·434
3·9	1·762	2·165	8·9	1·347	1·810	13·9	1·085	1·593	18·9	0·882	1·431
4·0	1·751	2·154	9·0	1·341	1·804	14·0	1·080	1·590	19·0	0·878	1·428
4·1	1·739	2·144	9·1	1·335	1·799	14·1	1·076	1·586	19·1	0·874	1·425
4·2	1·728	2·135	9·2	1·329	1·794	14·2	1·071	1·583	19·2	0·871	1·422
4·3	1·717	2·125	9·3	1·323	1·789	14·3	1·067	1·579	19·3	0·867	1·420
4·4	1·706	2·116	9·4	1·317	1·784	14·4	1·063	1·575	19·4	0·863	1·417
4·5	1·695	2·106	9·5	1·311	1·779	14·5	1·058	1·572	19·5	0·860	1·414
4·6	1·685	2·097	9·6	1·305	1·774	14·6	1·054	1·568	19·6	0·856	1·411
4·7	1·675	2·088	9·7	1·299	1·769	14·7	1·049	1·565	19·7	0·852	1·408
4·8	1·665	2·080	9·5	1·293	1·765	14·8	1·045	1·561	19·8	0·849	1·405
4·9	1·655	2·071	9·9	1·287	1·760	14·9	1·041	1·558	19·9	0·845	1·403
5·0	1·645	2·063	10·0	1·282	1·755	15·0	1·036	1·554	20·0	0·842	1·400
5·1	1·635	2·054	10·1	1·276	1·750	15·1	1·032	1·551	20·1	0·838	1·397
5·2	1·626	2·046	10·2	1·270	1·746	15·2	1·028	1·548	20·2	0·834	1·394
5·3	1·616	2·038	10·3	1·265	1·741	15·3	1·024	1·544	20·3	0·831	1·391
5·4	1·607	2·030	10·4	1·259	1·736	15·4	1·019	1·541	20·4	0·827	1·389
5·5	1·598	2·023	10·5	1·254	1·732	15·5	1·015	1·537	20·5	0·824	1·386
5·6	1·589	2·015	10·6	1·248	1·727	15·6	1·011	1·534	20·6	0·820	1·383
5·7	1·580	2·007	10·7	1·243	1·723	15·7	1·007	1·531	20·7	0·817	1·381
5·8	1·572	2·000	10·8	1·237	1·718	15·8	1·003	1·527	20·8	0·813	1·378
5·9	1·563	1·993	10·9	1·232	1·714	15·9	0·999	1·524	20·9	0·810	1·375
6·0	1·555	1·985	11·0	1·227	1·709	16·0	0·994	1·521			
6·1	1·546	1·978	11·1	1·221	1·705	16·1	0·990	1·517	21·0	0·806	1·372
6·2	1·538	1·971	11·2	1·216	1·701	16·2	0·986	1·514	22·0	0·772	1·346
6·3	1·530	1·964	11·3	1·211	1·696	16·3	0·982	1·511	23·0	0·739	1·320
6·4	1·522	1·957	11·4	1·206	1·692	16·4	0·978	1·508	24·0	0·706	1·295
6·5	1·514	1·951	11·5	1·200	1·688	16·5	0·974	1·504	25·0	0·674	1·271
6·6	1·506	1·944	11·6	1·195	1·684	16·6	0·970	1·501	26·0	0·643	1·248
6·7	1·499	1·937	11·7	1·190	1·679	16·7	0·966	1·498	27·0	0·613	1·225
6·8	1·491	1·931	11·8	1·185	1·675	16·8	0·962	1·495	28·0	0·583	1·202
6·9	1·483	1·924	11·9	1·180	1·671	16·9	0·958	1·492	29·0	0·553	1·180
7·0	1·476	1·918	12·0	1·175	1·667	17·0	0·954	1·489	30·0	0·524	1·159

APPENDIX A (*cont.*)

q %	x	a	q %	x	a	q %	x	a	q %	x	a
30·0	0·524	1·159	35·0	0·385	1·058	40·0	0·253	0·966	45·0	0·126	0·880
31·0	0·496	1·138	36·0	0·358	1·039	41·0	0·228	0·948	46·0	0·100	0·863
32·0	0·468	1·118	37 0	0 332	1·020	42·0	0·202	0·931	47·0	0·075	0·846
33·0	0·440	1·097	38·0	0·305	1·002	43·0	0·176	0·913	48·0	0·050	0·830
34·0	0·412	1·078	39·0	0·279	0·984	44·0	0·151	0·896	49·0	0·025	0·814
35·0	0·385	1·058	40·0	0·253	0·966	45·0	0·126	0·880	50·0	0·000	0·798

For incidences (q) over 50 %, take the tabulated value of x corresponding to $1-q$, but give it a negative sign: take the tabulated value of a corresponding to $1-q$ and multiply this by $(1-q)/q$, retaining the positive sign.

APPENDIX B

Summary of formulae for computing the regression, b, of relatives on propositi in respect of liability, and the sampling variance, V_b, of the estimate

The heritability, h^2, is given by $h^2 = 2b$, when the relatives are full sibs, parents, or children of the propositi, and the standard error of the estimate of the heritability is $2\sqrt{V_b}$. The quantities x and a are obtained from the table (Appendix A) and correspond to the observed incidence denoted by the subscript. Subscripts outside the brackets refer to all the quantities within the brackets. Other symbols are: q = observed incidence; $p = 1-q$; A = number of affected individuals in the sample from which the incidence is calculated: $a' = a\left(\frac{p-q}{p}\right)$ where q is the incidence from which a is derived;

$$W = p/a^2A$$

where p, a, and A correspond to the incidence denoted by the subscript to W. Each of the four methods is based on different observed incidences, as indicated.

Observed incidences and subscripts denoting them

General population, comparable with affected individuals g
General population, comparable with relatives gr
Relatives of normal controls c
Relatives of affected individuals r

Method 1. Two incidences: g and r

$$b = \frac{x_g - x_r}{a_g}, \quad V_b = [1/a - b(a-x)]_g^2 W_g + (1/a)_g^2 W_r.$$

Method 2. Two incidences: c and r.

$$b = \frac{p_c(x_c - x_r)}{a_c}, \quad V_b = [p/a - b(a'-x)]_c^2 W_c + (p/a)_c^2 W_r.$$

Method 3. Three incidences: g, gr and r

$$b = \frac{x_{gr} - x_r}{a_g}, \quad V_b = [b(a-x)]_g^2 W_g + (1/a)_g^2 (W_{gr} + W_r).$$

Method 4. Three incidences: g, c and r

$$b = \frac{p_g(x_c - x_r)}{a_g}, \quad V_b = [b(a'-x)]_g^2 W_g + (p/a)_g^2 (W_c + W_r).$$

APPENDIX C

Sampling variance of the estimate of the regression of relatives on propositi

The regression coefficient is estimated from two or three observed incidences, the sampling variances of which are independent of each other. The sampling variance of the regression can therefore be obtained from the partial differentials, uncomplicated by covariance terms. It is convenient to take the partial differentials with respect to the normal deviate (x) rather than the incidences. Then if w, x, and y are the normal deviates corresponding to three observed incidences, and b is the estimated regression coefficient

$$\partial b = \frac{db}{dw}\partial w + \frac{db}{dx}\partial x + \frac{db}{dy}\partial y,$$

and the sampling variance is

$$V_b = \left(\frac{db}{dw}\right)^2 V_w + \left(\frac{db}{dx}\right)^2 V_x + \left(\frac{db}{dy}\right)^2 V_y.$$

The population sampled is defined as being normally distributed with respect to liability. The following symbols will be used for the parameters of a normal distribution:

q = frequency of affected individuals (= incidence),
p = $1-q$,
x = normal deviate (single-tailed) corresponding to q, (w and y will also be used for normal deviates, in order to avoid subscripts),
z = height of the ordinate at deviation x,
a = z/q (= mean deviation of affected individuals),
N = number of individuals in the sample from which q is estimated,
A = observed number of affected individuals in the sample.

The following differential coefficients of the above parameters will be needed:

$$dq/dx = -z,$$
$$dp/dx = z,$$
$$dz/dx = -zx,$$

Since

$$a = z/q,$$
$$da/dx = (-qzx+z^2)/q^2 = a(a-x).$$

The sampling variance of the normal deviate, x (or w or y) is also required. This can be easily derived from the sampling variance of the incidence, V_q, thus:

$$V_x = \left(\frac{dx}{dq}\right)^2 V_q$$
$$= \left(\frac{-1}{z}\right)^2 \frac{pq}{N}$$
$$= \frac{p}{a^2 A}.$$

Here, of course, the values of p, a and A are those corresponding to the particular deviate, w, x or y, whose variance is required.

The formula to be used for estimating the regression differs according to the number of incidences observed, and the form of the variance depends also on which particular incidence is used to evaluate a. In order to avoid subscripts the following symbols will be used for the normal deviates corresponding to the different observed incidences:

Normal deviate	Derived from incidence in	Symbol used in text
w	Control relatives	x_c
x	General population	x_g or x_{gr}
y	Relatives of affected individuals	x_r

Method 1 (equation (2) of text). Two incidences: a evaluated from general population.

$$b = \frac{x_g - x_r}{a_g} = \frac{x-y}{a}$$

(a and x derived from the same observed incidence).

$$\begin{aligned}\partial b &= \frac{db}{dx}\,\partial x + \frac{db}{dy}\,\partial y \\ &= \frac{a-(x-y)a(a-x)}{a^2}\,\partial x + \frac{-1}{a}\,\partial y \\ &= \left[\frac{1}{a} - b(a-x)\right]\partial x + \frac{-1}{a}\,\partial y.\end{aligned}$$

Therefore

$$V_b = \left[\frac{1}{a} - b(a-x)\right]^2 V_x + \left[\frac{1}{a}\right]^2 V_y.$$

(Expressions for V_x and V_y have been given above.)

Method 2 (equation (4) of text). Two incidences: a evaluated from relatives of normal control individuals.

$$b = \frac{p_c(x_c - x_r)}{a_c} = \frac{p(w-y)}{a}$$

(p, a, and w derived from the same observed incidence). Put $B = (w-y)/a$, and note that $B = b/p$, and that the differentials of B are those of b in Method 1, but with w in place of x. Then

$$\begin{aligned}\partial b &= \frac{db}{dw}\,\partial w + \frac{db}{dy}\,\partial y \\ &= \left[p\left\{\frac{1}{a} - B(a-w)\right\} + Baq\right]\partial w + \frac{-p}{a}\,\partial y \\ &= \left[\frac{p}{a} - b\left\{\frac{a(p-q)}{p} - w\right\}\right]\partial w + \frac{-p}{a}\,\partial y.\end{aligned}$$

Therefore

$$V_b = \left[\frac{p}{a} - b\left\{\frac{a(p-q)}{p} - w\right\}\right]^2 V_w + \left[\frac{p}{a}\right]^2 V_y.$$

The derivations for the two remaining methods are similar and need not be given in full.

Method 3 (equation (5) of text). Three incidences: two different samples of the general population.

$$b = \frac{x_{gr} - x_r}{a_g} = \frac{w-y}{a}$$

(a derived from the incidence corresponding to x as normal deviate).

$$\begin{aligned}\partial b &= \frac{db}{dx}\,\partial x + \frac{db}{dw}\,\partial w + \frac{db}{dy}\,\partial y, \\ V_b &= [b(a-x)]^2 V_x + \left[\frac{1}{a}\right]^2 [V_w + V_y].\end{aligned}$$

Method 4 (equation (6) of text). Three incidences: as method 3, but with one sample of the general population replaced by control relatives.

$$b = \frac{p_g(x_c - x_r)}{a_g} = \frac{p(w-y)}{a}$$

(p and a derived from incidence corresponding to x as normal deviate).

$$V_b = \left[b\left\{\frac{a(p-q)}{p} - x\right\}\right]^2 V_x + \left[\frac{p}{a}\right]^2 [V_w + V_y].$$