M.Sc. ABSTRACT Genetics (Biology)

AN EMPIRICAL SIMULATION OF QUASI-CONTINUOUS INHERITANCE USING HUMAN BIRTHWEIGHT DATA

by

Benjamin K. Trimble

This study was an attempt to test models of continuous traits derived by Edwards (1960) and Falconer (1965). The data comprised some 400,000 weights of single live births recorded in British Columbia between 1946 and 1963. Means and variances of birthweight and correlations with parity, gestation length, and parental ages were similar to published results.

Arbitrary thresholds were imposed on a distribution of birthweights to generate "extreme birthweight" as a quasi-continuous trait. Observed risks to relatives of probands were compared to Edwards' prediction that the risk to sibs of probands equals the square root of the population incidence of the trait. Also, regressions of birthweights of relatives on birthweights of probands were compared to coefficients derived from Falconer's equation using population incidence and risks in sibs.

Edwards' prediction overestimated observed risks by about twenty percent. This poor fit was attributed partly to the low heritability of birthweight. Falconer's theorem could not be tested because no transformation was found to normalize the distribution of birthweights. His method was found to be very sensitive to departures from normality. It was concluded that the two models are generally not applicable to biological data since they are likely to lead to very unreliable predictions.

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INTRODUCTION

Diseases known to be due to single genes affect about 1% of liveborn individuals at some time in their lives. Examples are manifold and include such traits as achondroplasia, albinism and haemophilia. A further 1% of liveborn humans are affected by diseases, such as Down's syndrome, which are due to chromosomal aberrations. These two categories exclude, however, a large part of man's hereditary ill-health. About 2.5% of the population suffers or dies as a result of various congenital malformations and more than 1.5% from constitutional and degenerative diseases. Most of these traits are not simply inherited. Examples include spina bifida, diabetes and exophthalmic goiter. Thus, the diseases with complex inheritance account collectively for more than four times the inherited ill-health of our species than do the single gene traits.

It became apparent in the early 1950's that there was a type of inherited trait which was neither strictly Mendelian nor continuous and this type was termed "quasi-continuous." These quasi-continuous traits are phenotypically discontinuous and show strong familial correlations but they do not fit any patterns of Mendelian inheritance. It has been postulated that, although the phenotypic expression of the trait is discontinuous, the trait possesses a continuous aspect which can be thought of as the "liability", or the combined genetic and environmental susceptibility to the trait. Individuals with a liability greater than a certain threshold value will exhibit the trait, while individuals with

liability values below the threshold will appear "normal" (assuming that the threshold is greater than the mean liability). It is presumed that the distribution of liability is the consequence of many genes interacting with each other and with the environmental effects. Generally, liability is not measurable.

This concept of quasi-continuous inheritance has been applied to man in attempts to account for many of the troublesome diseases whose mode of inheritance is not known. On the basis of the conceptual model described above, theoretical analysis has led to two specific predictions: 1) the risk to relatives of a proband, with such a trait, is a simple approximate function of the population incidence of the trait and of the degree of relationship between the proband and relatives under consideration; and 2) the heritability of the trait can be expressed as an approximate function of the population incidence of the trait, of the degree of relationship between the proband and relatives being considered, and of the observed risk to relatives.

In view of the increasing use of genetic counselling with respect to human diseases and of the fact that many human diseases are assumed to be quasi-continuous traits, it seemed most desirable that the theoretical predictions be tested empirically.

One possible test requires family data for the whole of a large population with observations of a continuous trait that shows strong familial correlations. Birthweight is a good example of such a trait since it is routinely recorded for all progeny of every family and because birthweights

are known to exhibit strong familial correlations. Given such a body of data, one can let birthweight represent the liability of a quasi-continuous trait and simulate such traits by imposing arbitrary thresholds (any value within the range of observed birthweights may be chosen) and by designating all individuals with a birthweight on the same side of the mean as the threshold, but further from it, as expressing the trait and all other individuals as being unaffected. By calculating the empirical risks to relatives and the heritability of the trait, as a function of the regression of birthweights of relatives on birthweights of probands, a comparison of these values with the predicted values would then afford a simple test of the predictive reliability of the theoretical expectations.

The purpose of this report is to give the results of such a test of Edwards' (1960) prediction of sib risks for quasi-continuous traits and of Falconer's (1965) estimate of heritability for quasi-continuous traits. Edwards predicted that the risk to n^{th} degree relatives for a quasi-continuous trait, with a population incidence of p, would be about $\sqrt[n]{p}$. Falconer derived the equation $h^2 \doteq (Xg - Xr)/c$ where: 1) h^2 is the heritability of the trait, 2) Xg and Xr are the normal deviates corresponding to the incidence in the general population and relatives respectively, and 3) c is the ordinate at Xg. The tests were carried out with a very large body of human data that included birthweight records.

HISTORICAL SURVEY

a) Quasi-continuous Inheritance:

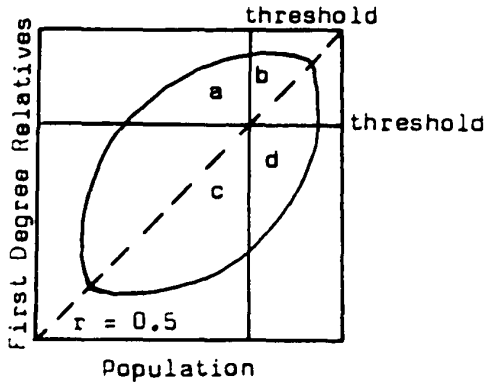
Using laboratory crosses between two inbred strains of mice (CBA and C57BL), Grüneberg studied the inheritance of both a tooth defect (absence of a third molar) and a number of skeletal characters (notably, foramen acetabuli perforans) but could find no simple genetic interpretation for the variability in either trait despite strain-specific incidences of the traits. He concluded, however, that the results were consistent with a model whereby these (more or less) "discontinuous anomalies are phenomena which tend to arise near the extremes of continuous (and so far unidentified) distributions" (Grüneberg, 1952). He found that the sizes of third molars, or their rudiments, were determined physiologically and that there was an increasing probability of absence as the size of the tooth decreased (Grüneberg, 1951). Thus, absence of a third molar is a discontinuous trait determined by some continuous physiological variable and a dichotomizing threshold. He later proposed the term "quasi-continuous" for such traits and found that several of the skeletal anomalies in mice gave results indicating that they too were quasi-continuous traits. He concluded further that the underlying continuous variables were a consequence of multiple additive genetic effects and that they were sensitive to environmental influences (Grüneberg, 1952).

The ratio, K, of familial to population incidence of a trait is generally interpreted as an indicator of hereditary causation (i.e., $K \geq 10$). Penrose (1953) showed that a low value of K (i.e., $1.5 \leq K \leq 4.5$) does not necessarily indicate a lack of hereditary causation but rather

that if the trait has an hereditary background, the causative gene or genes must be very common in the population. For acute rheumatic fever, he obtained K = 1.5 and showed that if the cause were a single gene, this gene must be prevalent enough for nearly half the population to be susceptible to the disease with its actual frequency being determined by environmental causes. A more attractive hypothesis is that traits with low K values are quasi-continuous traits. In this instance, many additive genes may all be present in the population at an equal and high frequency but still give rise to a low incidence in the population. Further, twin data on rheumatic fever give a much higher K value for monozygotic twins than for sibs as expected for quasi-continuous traits (Penrose, 1953). Finally, he points out that values of K for different degrees of susceptibility can be calculated from tables of tetrachoric functions if one assumes that the trait in question is quasi-continuous, in the sense proposed by Grüneberg, and that the genotypic correlation between proband and sibs is 0.5. Thus, we have reason to consider the hypothesis of quasi-continuous variation as an attractive one for many of the common diseases of man (those with low K values and without evidence of simple Mendelian inheritance).

Expanding on Penrose's work, Edwards (1960) considered the case of multiple additive genes and an abrupt threshold with a proportion, $\underline{p}$, of the population lying beyond it. He further assumed that the genotypic correlation between n^{th} degree relatives was about $(1/2)^n$. He referred to the bivariate normal surface, as drawn below, and showed that $\ln(bc/ad) \doteq (8/pi)\tanh^{-1}\underline{r}$ where $\underline{r}$ is the genotypic correlation coefficient

(Edwards, 1960). Assuming that both thresholds are equidistant from the mean, he used this approximation to demonstrate that the risk to first degree relatives is approximately $p^{1/2}$. Moreover, this approximation consistently underestimates the risk read from tables of tetrachoric functions when p is less than about 16% and it over-estimates for higher values of p. Edwards also pointed out that the risk to an



unborn increases with the number of affected relatives in the case of multifactorial traits but remains constant in case of single gene traits.

In a study of first degree relatives of probands with congenital pyloric stenosis (an hypertrophy of the circular muscle layer of the gastric pylorus), Carter (1961) obtained the following results: 1) the risk to offspring exceeded that to sibs, 2) several male probands had affected sons, 3) although the population incidence among females was much lower than among males, the risk to relatives of female probands was greater than that to relatives of their male counterparts and, 4) the

increase in the proportion of affected relatives was higher for female relatives of probands compared to the incidence in the general population of the same sex. Since the first two results make it unlikely that a recessive or sex-linked component is important in the genetic causation of the trait, and since a single dominant hypothesis can be ruled out right away, Carter proposed that susceptibility to congenital pyloric stenosis is due to a dominant gene common to both sexes and sex-linked multifactorial inheritance. He also felt that the multifactorial component might be related to general body musculature but he gave no evidence on this point. Finally, it is interesting to note that the observed risks in this study are consistent with Edwards' square root prediction for male sibs of male probands but they are somewhat too high for female sibs of female probands. However, Carter's small sample sizes make such numerical comparisons rather unreliable. Carter's is the first study of a human disease, that the author is aware of, in which quasi-continuous inheritance is postulated to be a major component of the genetic causation of the disease.

The conclusion that an important component in the genetic causation of some human diseases is quasi-continuous was extended to cover other common malformations, notably congenital dislocation of the hip, cleft palate with or without cleft lip, clubfoot, and malformations of the central nervous system, specifically spina bifida and anencephaly (Carter, 1963).

In a paper on the genetic basis of common disease, Edwards (1963) suggested that there is an intrinsic difference between the genetic basis

of rare and common familial diseases, the former being due generally to single gene effects of high specificity and the latter to a multifactorial aggregate each giving rise to a distribution of liability for a disease. In a discussion of concepts involved in the genetics of disease, he not only postulated this quasi-continuous basis for common diseases but also explained the need for new methods of genetic analysis of diseases with an incidence of about one percent or greater. As well, he emphasized the possible pitfalls of using the methods which were so successful in the study of rare diseases.

An effect of inbreeding on quasi-continuous traits, even when no assumptions about dominance or heterozygous advantage are made, may be expected since hidden variability becomes exposed as phenotypic variation. Newcombe (1964a, b) pointed out that since inbreeding reduces the number of freely assorting factors, it flattens the frequency distribution and extends the tails in both directions. Extension of the tails will cause an increase in incidence of quasi-continuous traits.

Newcombe (1964b) further noted that a graph of the increase in incidence in relatives plotted against the general population incidence, done for a large number of hereditary diseases, shows these conditions to fall mostly into two discrete groups. These groups would seem to fit the class of single factor traits for the one and what would be expected for multifactorial inheritance for the other with very little overlap between the two. This graphic method provides a first indication of which human diseases are quasi-continuous and it implies that in this group of diseases

there is little contribution from the effects of single major genes.

With the concept of quasi-continuous variation as a likely model for many of the human diseases widely accepted, Falconer (1965, 1967) derived heritability estimates for such traits from their population incidence and the observed risk to n^{th} degree relatives. In Falconer's model, the underlying continuous distribution includes the environmental as well as the genetic components which contribute to an individual's likelihood to develop the disease in question. Moreover, so as to use the standard deviation as the unit of measurement, he assumed that the scale of measurement gives rise to a normal distribution of the underlying variate and, therefore, that the genetic component of the disease would be multifactorial or, if few genes were affecting the trait, that each would have a small effect relative to the nongenetic variation. Falconer realized that data such as two disease incidences lead to mean measures of the underlying variate analagous to those of standard "selection experiments" of quantitative genetics (Falconer, 1960) and thus that the methods of quantitative genetics can be employed to obtain a regression of relatives on propositi for the underlying variate and from this an heritability estimate. For the simple case of an incidence in the general population having a normal deviate of X_g and an ordinate value of $\underline{c}$ and a corresponding deviate of X_r for first degree relatives, the regression equals $(X_g - X_r)/c$. In the first paper (Falconer, 1965), the general method was developed to estimate the correlation between relatives from the known incidences from which estimates of the relative importance of hereditary causes of differences

between individuals could be derived. He applied this method to four examples from published data and obtained heritability (± standard error) estimates ranging from 37 ± 6% for peptic ulcer to 79 ± 5% for congenital pyloric stenosis. Further, he worked out a table of normal deviate and ordinate values by percent incidence and pointed out how the method could be used to predict incidences, not known by direct observation, which could be useful in genetic counselling.

In his later paper, Falconer (1967) extended his method to diseases with a variable age of onset and applied the new development to published data on diabetes mellitus. He obtained an overall heritability of 35% but found a decrease of heritability estimates with increasing age. He attributed the latter effect to an increasing mean value of the underlying variate as well as to increased environmental variation.

Morton (1967) presented an hypothesis for discriminating between the segregation of major genes and continuous additive gene action. Detection of a major gene by this method would disprove an hypothesis of quasi-continuity while failure to detect a major gene would be insufficient to prove the hypothesis. Thus, this approach was presented as an alternative to quasi-continuity which remains extremely difficult to disprove. He also compared the theorems of Edwards and Falconer and pointed out that "Edwards' theorem overestimates Gr (the sib risk) by about 5% for $h^2 = 0.1$ and that the relative error increases with h^2."

Edwards (1967) proposed an alternative hypothesis whereby the underlying

variable would be a measure of the genetic variability only. Then the threshold, rather than being abrupt, would be a function of the genetic variability. He chose an exponential form to represent this "risk" function (i.e., $g(x) = ae^{bx}$) where the underlying variable, x, is assumed to be normally distributed.

Elston, Campbell and Morton (see Campbell, 1969) extended this model, using a truncate normal distribution of genetic variability, and found that the probability that an individual, with a genotypic value of x, would manifest the trait is given by $g(x) = e^{b(x-c)}$ where: 1) a is the value of the threshold, 2) $x \leq c$ and 3) b is an estimate of mean genotypic value (measured in terms of standardized normal variates) from observed incidences of the trait. They also found, in applying their model to published data on human diseases, that c was invariant for any specific disease and that for all diseases tested, its range was restricted to about 3.25 to 4.5 standard deviations above the mean.

In a recent paper Morton et al. (1970) derived expectations for inbreeding and recurrence risks under three models of multifactorial inheritance: Falconer's abrupt threshold model, Edwards' exponential threshold model, and the "Morton-Crow-Muller" genetic load model. Data of eight human diseases were examined of which four (deaf mutism, limb girdle muscular dystrophy, severe mental defect, major malformations) gave a significantly bad fit under all three models; they are known from other studies to have a component due to rare recessive genes so that multifactorial models do not apply to them. The other four traits (talipes equinovarus, peptic ulcer, low ridge count,

pyloric stenosis), however, gave no evidence of non-additivity of gene effects; they were fitted best by Falconer's model but they agreed also with Edwards' model and with the discontinuous model of genetic load theory. Morton et al. (1970) concluded that "our results show that it is exceedingly difficult, and may be practically impossible, to infer the genetic basis of traits which do not give regular mendelian ratios." This result reflects the difficulty inherent in studies of the genetic basis of genetically complex traits, but it does not imply that quasi-continuous traits do not exist in nature.

In a later review paper, Edwards (1969) pointed out that given a model with an abrupt threshold, any approximation to normality declines rapidly as we deviate from the center of the distribution so that the approximation is unlikely to be good for a threshold lying beyond two standard deviations from the mean. Moreover, with an exponential risk function, environmental effects will shift distributions in inconsistent ways such that it becomes very difficult to assess these influences and their major effects on familial concentration.

Despite the intrinsic difficulties in arriving at a tractable, formal model for quasi-continuous traits, Carter (1969) considered these models the best that we have to describe and analyze many of the common human diseases such as cleft lip and palate, pyloric stenosis and others mentioned earlier.

The analytical methods discussed above have recently seen a resurgence of interest in application. One example is the test for racial differences

in incidence of talipes equinovarus (Ching et al., 1969) assuming the trait to be quasi-continuous. In this analysis, Ching and his colleagues found that the additive effects of both Hawaiian and Oriental parents were highly significant with respect to the calculated underlying variable derived from incidences using Falconer's methods. Simpson (1969) applied Falconer's model to obtain heritability estimates for diabetes mellitus. Estimates of heritability were consistently near 0.5 for males of all ages while those for females declined from about 0.5 at age 50 to 0.2 at age 80. As well, sex differences were observed among affected relatives, at high ages of onset independent of the sex of propositi, which did not have a genetic explanation. Campbell (1969) tried to fit the model of quasi-continuous variation derived by Morton to sets of data on three human traits. Using Hawaiian records on all surgically corrected cases of pyloric stenosis occurring in the period 1942 to 1966 and further following data, she obtained a fit which was neither good nor consistent over subsamples. Hypercholesterolemia data, from a random sample of 7000 adult Japanese males, gave evidence of a dominant major gene and consequently a poor fit to the quasi-continuous model. Finally, defining a dermal ridge count of zero as affected, Campbell obtained a good fit to the model for a large body of family data on dermal ridge count. Since dermal ridge count is accepted as being additive and multifactorial (Holt, 1968), this is reassuring to those who accept the quasi-continuous models as accurate abstractions of Grüneberg's biological concept. In a review paper on cleft lip and palate (Fraser, 1970) which is the summation of a workshop on the subject, it is

concluded that the accumulating evidence favours a quasi-continuous model for the inheritance of these malformations. In the case of isolated cleft palate, the underlying variable appears to be the developmental stage at which the palate shelves move from a position lateral to the tongue to a horizontal plane above the tongue (Fraser et al., 1957). The recurrence risk to siblings was found to fit closely Edwards' square root prediction. Also, relative increases of risk between different degrees of relatives and increasing risk with increasing number of affected relatives were as expected with a quasi-continuous, abrupt threshold model. One last example of the application of quasi-continuous models is the use of Falconer's theorem to estimate heritabilities for different types of epilepsy (Andermann and Metrakos, 1970). For each type of epilepsy studied, they caclulated mean liabilities and heritabilities for each sex and age group. They then used these values to determine recurrence risks for various degrees of relatives and concluded that "this approach should have useful applications for genetic counselling."

The concept of quasi-continuity, then, seems to be a reasonable hypothesis for many of the human traits which formerly afforded no simple genetic explanation and one which is becoming increasingly applied by a number of different workers.

b) Birthweight:

The classic studies on the inheritance of human birthweight are reported in a series of papers in the early 1950's by Karn, Penrose and their colleagues. In the first report from a survey of a large body of medical data (Karn and

Penrose, 1951), it was found that sib correlations for birthweight were close to 0.5, indicating a hereditary basis for the trait, and also that the probability of prematurity (birthweight less than 5.5 lbs.) is much increased in sibships with an earlier born premature sib. The mean weight of liveborn males was about 3314 grams and that of females about 3223 grams.

After analyzing nearly 14,000 birth records (Karn and Penrose, 1951), they concluded that birthweight increases with parity but decreases slightly with mother's age where maternal age and parity had a correlation of 0.5. From survival rates, they found that the most favourable weight was nearly 3732 grams, much above the mean weight. Also, birthweight was correlated with gestation length to the extent of 0.4.

In an analysis of 315 twin births which were a part of the survey, it was found that the unlike-sexed group had a generally higher birthweight and smaller standard deviation than the like-sexed group. Other associations with weight were found to be the same as in the analysis of single births (Karn, 1952).

In a study of twin data originating from a different geographical region, Karn (1953) found that weight increased with parity up to the fourth birth order after which it remained constant. Unlike single births, these twin births showed a small but positive correlation of weight with mother's age. Otherwise, associations were the same as in the previous studies (Karn, 1953).

A study of birthweight in cousins showed a significant positive correlation between birthweights of maternal first cousins but not between

other first cousins (Robson, 1955). This indicated a strong maternal component. Estimates of the components of the phenotypic variance in birthweight were as follows: maternal heredity = 0.20, maternal environment = 0.32, foetal genotype = 0.18 and residual variation = 0.30.

Morton (1955) studied Japanese data on half sibs, twins, full sibs and consanguineous matings, using material collected by the Atomic Bomb Casualty Commission. From this study, he also concluded that the resemblance in birthweight of sibs is primarily due to the maternal genotype and intrauterine environment and not to genotypic similarity of sibs. He found no significant effect of inbreeding on the variance of birthweight or on the correlation between sibs. Foetal inbreeding, however, did cause a decrease in mean birthweight.

In a preliminary record linkage study, Hobbs (1963) reported on births from some 22,000 women. As with earlier studies, the sib correlation for birthweight was near 0.5 and the risk of prematurity increased greatly when there was already a premature birth in the sibship.

A study of the relationship between birthrank, as opposed to birth order (weights are ranked from heaviest = 1 to lightest), James (1969) showed that the increase in weight is roughly linear after the second birth rank for all families combined and that for ranking within individual sibships, there is an increase, although not linear, of birthweight with rank up to the fifth rank after which weight stays fairly constant.

MATERIALS AND METHODS

The data used derive from vital statistics records relating to children born in the Canadian province of British Columbia over the thirteen-year period 1951-1963. A total of 535,146 births were available of which 455,785 were singleton livebirths. These birth records had previously been linked to a file of family records which included a marriage, when the place of marriage was British Columbia, followed by livebirths and stillbirths of siblings grouped together in order of birth dates (Newcombe, 1964; Kennedy et al., 1965).

In creating this master-file, inconsistencies and changes in people's names led to the inclusion of extraneous records. Procedures were implemented to avoid most of the resultant artificial inflation of the tabular information (Smith et al., 1965). Moreover, it has been found that the unavoidable redundancy leads to less than 1 percent inflation of the data in a manner which does not introduce biases (Newcombe, 1966).

A number of steps were involved in the extraction of the relevant data from the master-file:

a) production of one 25-word record per family, with trailing records when there were more than 6 sibs in the family,

b) derivation of sibship summaries of one word for each singleton livebirth that had a recorded birthweight and

c) extraction of tabular and statistical information from the sibship summaries.

Analysis was restricted to birthweights in families containing only singleton livebirths where the weights fell within the range of 500 to 6500 grams. Thus, it is presumed that the analysis was restricted to normal variation in birthweights.

Weights on the source documents were recorded to the nearest ounce (1957-1959), or the nearest gram (1951-1957 and 1960-1963), or the nearest 250-gram unit (1959-1960). In deriving the sibship summaries, all results were converted to the nearest 250-gram unit for the maximum homogeneity of the weight recordings. This resulted in 24 possible weight classes.

In all 210,950 male and 201,150 female weights were analyzed (Appendix, A1 - A3).

The first step in the analysis of the data was to obtain a profile of the population under investigation by computing frequency distributions of birthweights by sex and by birth order. Statistics such as sample size, mean, variance and measures of normality were obtained for each distribution. The frequency distribution of family size and its mean and variance were also calculated.

In simulating quasi-continuous traits, thresholds were imposed at the midpoint of each weight class in order to test the predictions over a wide range of incidences of a trait. Consequently, the first step was to determine the distance of the thresholds from the mean and the corresponding

incidences of the trait. This was done for males and females separately.

Because birthweight is known to increase with birth order, three methods of ascertainment were used to calculate sib risks:

a) ascertainment through the first born child in the family,

b) complete ascertainment (every affected individual is a proband and families are counted as often as they contain probands) and

c) ascertainment through the last born child in the family.

Because of the increase of birhtweight with increasing birth order, a) and c) are expected to set upper and lower limits to sib risks for data unadjusted for parity in the following manner: first, for thresholds below the mean, a trait (i.e., birthweight $<$ threshold) would have a lower predicted risk (as obtained from Edwards' square root prediction) when ascertainment is through the last born child and a higher predicted risk when ascertainment is through the first born child compared to data adjusted for parity. The opposite is expected for the observed incidences; second, for thresholds above the mean, a trait (i.e., birthweight $>$ threshold) would have a lower predicted risk when ascertainment is through the first born child and a higher predicted risk when ascertainment is through the last born child, again compared to data adjusted for parity. As above, the opposite effect is expected for the observed incidences.

Complete ascertainment, (b), is expected to give intermediate predicted risks and observed incidences in all cases.

Using the three methods of ascertainment, predicted sib risks and observed incidences in sibs of probands were obtained at all 24 thresholds for male and female sibs of male and female probands, for male sibs of male probands and for female sibs of female probands. In all instances, the following values were also calculated: 100 (observed-expected)/expected, the ratio of observed to expected, and the chi-square value corrected for continuity when necessary.

The prediction of heritability for quasi-continuous traits rests on the assumptions that the scale of measurement used for the underlying variable gives rise to a Gaussian distribution and that the variance of relatives is the same as that in the general population. To assess the sensitivity of Falconer's method to deviations from normality, various transformations of the birthweight values were devised and departures from normality of the distributions of all transformed birthweights were tested separately for each transformation. The scales of measurement used were the following: a) $\log_{10}$ (birthweight/250 + 1); b) $\sqrt{\text{birthweight}/250 + 0.5}$; c) birthweight unchanged; d) an empirical transformation described below and e) 0.8625 (1 + 0.01153 (birthweight/250 - 12)^2) exp(-.01414 (birthweight/250 - 12)^2). It is expected from theoretical considerations that the logaritnmic transformation will change any skewness, $\underline{p}$, by a factor of approximately $1/(2\sqrt{p})$ and any kurtosis, q, by a factor of about 1/(3q). Similarly, it is expected that the square root transformation will change any skewness by about 1/(4p) and any kurtosis by about $1/(32p^2)$ (Kendall and Stuart, vol. 3). The empirical transformation, (d),

was obtained by first plotting on the same graph the observed frequency distribution and the expected normal distribution with the same mean and variance, multiplied by a constant so that the modal values of the two distributions coincided, then the graphic deviation was measured at each class interval between the observed and expected curves; lastly, the new values used at each class interval were (birthweight/250 + deviation). Consequently, the transformed distribution is expected to be more nearly normal with decreases in both skewness and kurtosis. The last transformation, (e), was obtained as follows: 1) plot the ratio of observed over expected against class values; 2) guess at a general equation from the graphic properties of a smoothed-out version of the distribution of ratios (i.e., $k(1 + b(x - c)^2 \exp(-a(x - c)^2)$; 3) determine the constant $\underline{k}$ as the maximum point on the curve where $\underline{c}$ is the abscissa for this point; 4) find the value of $\underline{b}$ in terms of $\underline{a}$ when the derivative of the equation is set to zero; and 5) find numerical values for $\underline{a}$ and $\underline{b}$ by determining the point of maximum slope graphically and solving the second derivative at this point. This transformation too ought to give a distribution more nearly normal in terms of both skewness and kurtosis than the observed distribution. These various transformations then give us distributions which will vary both further from (i.e, transformation (a)) and closer to (i.e., transformation (e)) normality than do the untransformed data. This should enable us to test the sensitivity of the method, for heritability predictions, to our range of deviations (i.e., skewness from +0.3 to -2.3 and kurtosis from -0.04 to +14.0) from normality.

Regressions of birthweights of relatives on birthweights of probands

were obtained next at all thresholds using Falconer's theorem and observed population incidences and incidences in sibs of probands. This was done separately by sex and with the sexes combined to obtain 24 coefficients for each sex category which will be referred to as "derived" regression coefficients. These were obtained only for the case of complete ascertainment. Also, the variances of relatives were calculated for male and female relatives of male and female probands, again, for complete ascertainment only. The variances of relatives were then compared to the variances of the population at each threshold.

Regression coefficients were also calculated from birthweight values for each threshold. The regressions of birthweights of relatives on birthweights of probands were obtained using a modification of the method devised by Kempthorne and Tandon (1953). This method makes the best use of all data by combining the sums of squares and cross products from families of different sizes according to a weighting factor appropriate to the family size and a guessed value of the coefficient to be estimated. The guessed values used were the product moment correlation coefficients between weights of probands and mean weights of their sibs divided by one minus the coefficient. Thus, the correlation coefficients between sibs and probands of either sex were calculated at all thresholds. Then, regression coefficients were determined at all thresholds and for each transformation with sexes separate and combined. In the case of untransformed data, mid-values of weight classes were used rather than actual weights. These regression coefficients obtained from birthweight values

will be referred to as "measured" regression coefficients. Finally, for each threshold-sex class, we have one derived regression coefficient to be compared to each of the five measured regression coefficients.

RESULTS AND DISCUSSION

The total number of families analysed was 220,489. Frequencies per family size (Appendix - A4) decrease rapidly from over 100,000 families of size one to only five families with more than thirteen children. The mean family size is about 1.9 and the variance is about 1.3. In a modern population, such as this, with its mixture of contraceptive and noncontraceptive groups as well as biological variations in fertility, "there is no reliable approximation to the distribution of family size, especially incomplete size " (Barrai et al., 1965). The best general distribution describing variation in family size was found by the same authors to be the truncated negative binomial distribution. No fit to this distribution was attempted for the present data since there is an obvious excess of families of size one. Family size here refers not to the actual family size but rather to the number of progeny in a family whose births and corresponding birthweights were recorded in the files. The excess of families of one, then, reflects three circumstances: a) births occurring in the late 1940's that represent the last birth in a family but the first entry for that family in the files, b) corresponding births in the 1960's that represent the first birth in a family where later births have yet to be added to the files, and c) families for which there were two or more records of births but where only one of the records included birthweight. Except for the excess of unitary families, the distribution of family size compares well with that from a current study

in Hawaii (M. P. Mi, personal communication).

The distribution of birth order (Appendix - A1, A2 and A3) similarly shows a rapid decrease in frequencies from low to high birth orders with a notable deficiency of children of birth order one. This deficiency likely is due to several circumstances: a) a possible tendency of mothers, especially from lower socio-economic groups and from rural areas, to give birth to their first child at home and in consequence there would be no recorded birthweight for this child, b) the large number of families included in the files where the first child was born prior to the initiation of the files, and c) other biases such as the immigration into British Columbia (which exceeds emigration) includes many families where the first child was born prior to immigration and consequently is not recorded in the files. Furthermore, the sex ratio varies non-linearly with birth order from 1.05 (males/females) for birth order one to 0.98 for birth order nine. Although no regression of sex ratio on birth order was calculated, it is clear that it would have a negative slope. Thus, the overall tendency would seem to be a higher probability of a male than female birth for lower birth orders to an equal probability for birth orders as high as nine.

The general distribution of birthweights (Appendix - A1, A2 and A3) is significantly leptokurtic and skewed somewhat to the left. The leptokurtosis statistic describes the fact that the distribution has a high narrow peak (i.e., narrower than the peak expected for a Gaussian distribution) but

wider than expected extension of low frequencies about the peak. The skewness statistic indicates that the curve is asymmetric with an excess of low birthweights. The Kolmogorov-Smirnov statistics are based on cumulative normal distributions and will detect deviations from normality other than (as well as) those due to kurtosis and skewness. A graph of the cumulative frequency distribution of these data, however, did not indicate any other types of deviations from normality. These characteristics (i.e., leptokurtosis and negative skewness) persist even when the data are broken down both by sex and by birth order. Since lower birth orders have generally lighter birthweights than later birth orders, some of the skewness can be ascribed to the excess of small families in the data. A more important cause of the skewness, however, would seem to be the fact that birthweight is highly correlated with gestation length ($r \doteq 0.4$) and the distribution of gestation length itself is strongly skewed to the left. This latter fact is not at all surprising since a woman can give birth even during the foetal stage of growth while biological determinants and modern medical practice combine to prevent her from carrying an embryo much beyond term. The leptokurtosis might well be due to stabilizing selection. Although the data deviate statistically from normality, "it is surprising to find such a bulk of biological data to fit a Gaussian distribution as closely as do these birthweights" (T. E. Reed, personal communication).

The general mean and standard deviation for the 412,100 recorded weights are 3354.4 grams and 549.5 grams respectively. The coefficient of variation is 16.38% for the combined data compared to 16.43% for male

birthweights and 16.07% for female birthweights. Males are 128.7 grams heavier than females overall and have a slightly larger variance. These results are extremely close to the published results, referred to earlier, of Karn and her colleagues.

As in the studies reviewed above, birthweight increases with birth order (Appendix - A1, A2 and A3) in a non-linear fashion up to birth order five beyond which there is no significant change although a small rate of increase is still evident. This holds for males and females both separately and together. Moreover, the mean difference in weight between males and females remains fairly constant over the range of birth orders. The observed variance also increases with birth order which is a reflection mostly of decreasing sample size.

Birthweight also increased with increasing parental ages. However, the correlation of birth order with parental ages was very high ($r = 0.75$) most of this correlation being due to the correlation of birth order with maternal age ($r = 0.48$ when paternal age is held constant). Birthweight was correlated to maternal age for birth order held constant only to the extent that $r = 0.07$. Thus, despite the increase of birthweight with parental ages, the increase is almost completely due to the high correlation of maternal age with birth order and the fact that birthweight increases with increasing birth order.

Sib-sib birthweight correlations were also high. The mean correlation coefficient was 0.45. The correlations for like-sexed sibs were 0.46 for

males and 0.47 for females. For unlike-sexed sibs, the correlation was naturally lower ($r = 0.42$). These results are also in good agreement with published estimates and differ little from the theoretical value of 0.50 expected for biometric traits when family environment is nearly random.

The thresholds (Appendix - A5) imposed to simulate quasi-continuous traits were all 24 possible mid-class values so that any individual with a birthweight more extreme than the threshold was considered to have the trait. Thresholds were set up for males and females combined as well as separately. Threshold values ranged from about 5 standard deviations below the mean to 5 standard deviations above the mean running at quite regular intervals of about 0.44 or 0.45 standard deviations in males and of about 0.47 to 0.48 units in females. The thresholds gave a range of frequency of "extreme" birthweights of about 5×10^{-4} to about 6.5×10^{-1}.

Three different methods of ascertainment were used to test Edwards' prediction that the risk to sibs of probands, who have a quasi-continuous trait which has a population incidence of p, is about $\sqrt{p}$. The purpose of using three different methods of ascertainment and their expected effects were discussed in the materials and methods section. The observed and predicted risks agree well with the expected relative effects of the different methods of ascertainment (Appendix - A6, A7 and A8) except that the predicted risks for thresholds below the mean are almost uniformly much higher than anticipated when ascertainment is through the last-born child in the family. This is almost certainly due to the excess of families of size one or two where most of the progeny including the last are of low birth order. This trend is the same whether males and females are treated

separately or not. Other than the consequences of this expected pattern of effects of ascertainment (i.e., when Edwards' prediction is an overestimator, then the degree of overestimation is least for ascertainment through the last-born child and greatest for ascertainment through the first-born), the data do not indicate any contribution to deviations of observed from predicted due to the method of ascertainment. The few discrepancies in the expected pattern of observed risks determined from the different methods of ascertainment can fairly be considered as due to sampling variation as a result of small sample sizes. It should perhaps be emphasized that this discussion has involved only risks from one ascertainment method relative to the other methods of ascertainment and says nothing about how well observed risks compare with predicted risks.

A comparison of the number of affected sibs predicted by Edwards' approximation with the observed number of sibs lying beyond the threshold is given by ascertainment method, sex, and threshold in tables A9 to A17. Analysis of the data separately by sex causes a decrease in chisquares but has no effect on the ratio of observed to predicted frequencies. While the chisquares are generally very large and the breakdown of the data by sex changes the significance of the values at only some of the extreme thresholds, the better fit of predicted to observed when males and females are analyzed separately is undoubtedly a real effect and not a statistical artifact. This is to be expected since analysis of the data with males and females pooled is in fact an analysis of two distinct quasi-continuous traits with different mean liabilities and different variances. The

nonsignificance of some of the chi-squares at extreme thresholds may be due to sampling variations where the sample sizes are quite small. Thus, while analyzing the data separately by sex does very much reduce chi-square values, the increased goodness of fit is insufficient to make Edwards' approximation reliable even when applied separately to each sex. This is true regardless of the method of ascertainment.

In terms of chi-squares, the deviations of predicted from observed values are not significant at some of the extreme thresholds (i.e., for $\alpha = .05$, thresholds 1 to 7 and 18 to 24 for females ascertained through the last-born) but are uniformly significant for thresholds in-between. It may be that the nonsignificant chi-squares at the extremes are due to sampling variations where the sample sizes are small. For complete ascertainment, Edwards' prediction is a consistent overestimate for thresholds 3 to 13 and, as expected, the degree of overestimation is less for ascertainment through the last-born and greater for ascertainment through the first-born. Outside this range, the prediction overestimates at all thresholds below the mean and it underestimates for thresholds above the mean where the incidence of the trait is small; there is a region (thresholds 14 to 19) where the deviations seem to depend on both sex and method of ascertainment. If the nonsignificant chi-squares at the extremes are due to sampling variations, nonsignificant deviations for thresholds 14 to 19, when they occur, might be expected by chance alone when deriving altogether some 180 chi-square values (i.e., by chance alone we expect 9 nonsignificant chi-squares on the assumption of lack of fit for all thresholds). The

predictions then consistently overestimate except at thresholds above the mean with incidences of about .01 or less. Here the predictions underestimate the risks. For intermediate incidences, the predictions are gross overestimates of the observed risks. The fact that the goodness of fit, in terms of chi-square values, decreases as the threshold approaches the mean from either side, is contrary to Edwards' (1960) claim that "the approximation becomes progressively less exact as the distance of the dichotomies from the center increases." This discrepancy is to some extent a function of sample size since the ratio of observed to predicted numbers deviates increasingly from unity as the threshold moves away from the mean. This ratio is approximately 0.60 at the mean. It reaches a low of 0.50 at the lowest threshold and a high of about 4.00 at the highest threshold. It is known that the approximation becomes progressively worse as the heritability decreases. Although the full sib correlations provide an upper estimate of heritability very near one, Robson (1955) has shown that heritability of birthweight is, in fact, about 18%. It is expected, therefore, that the relative error of the approximation is large because of the heritability of birthweight. Normality of the distribution of the underlying variate, which at present cannot be measured for real quasi-continuous traits, is not relevant to this application. The data are certainly continuous and, therefore, a transformation can be found, at least theoretically, which renders the distribution normal without in any way changing the frequencies of normal and affected individuals. This last fact holds because the threshold itself is a function of any transformation that might be used.

The conclusion is that even if there are human traits which are inherited according to Edwards' assumptions then his prediction is not sufficiently good for the prediction of risks to relatives for these traits unless the heritability of the underlying variable is close to one. For a heritability of about 0.20, Edwards' approximation overestimates the real risk to sibs by about 20% with the gradient of the error going from overprediction for thresholds below the mean to underprediction for thresholds two or more standard deviation above the mean where the incidence of the trait is about .01 or less. Because of the large sampling variation due to small sample sizes, it is not possible to determine the exact percentage of underprediction.

Although it was not necessary to find a transformation which normalized the frequency distribution of birthweights in order to test Edwards' approximation, this was not the case for Falconer's approximation. Falconer's theory rests on the assumptions that: a) the distribution of the underlying variate is Gaussian and b) either there is no difference in the variances between relatives and the general population or measurements are made in terms of standardized normal deviates. Since a test of the reliability of Falconer's approximation involves estimates of heritability which are sensitive to deviations from normality, a transformation giving a new distribution of the underlying variate that does not deviate significantly from normality is required. A search for such a transformation was performed for the present birthweight data (Appendix - A18). Although some transformations decreased the deviations from normality, none was found

for which the deviations were nonsignificant as measured by Fisher's g_1 and g_2 statistics or by the Kolmogorov-Smirnov test of normality. Five different transformations were then used to obtain regression coefficients in an attempt to find a functional relationship between goodness of prediction and degree of deviation from normality. These transformations give a range of skewness values from -2.34 to +0.28, of kurtosis from +13.97 to -0.04 and of the Kolmogorov-Smirnov statistic from +1.00 to +0.02. All of the values indicate significant deviations from normality but it is to be expected that the transformation which gives values closest to zero will provide measured regression coefficients that are closest to predicted coefficients if Falconer's theorem is reliable.

To test Falconer's theorem, only the method of complete ascertainment was used. As mentioned in the materials and methods section, this means that each "affected" sib in a family is considered a proband and each family is counted as many times as it has probands. Variances in birthweight of sibs of probands were obtained separately for each threshold and sex and with sexes pooled. These were then compared to the corresponding population variance (Appendix - A24). All F-ratios were statistically significant indicating that in all cases the variances of sibs differed from the variance in the population. Although these might be statistical artifacts for thresholds near the mean where sample sizes are very large, all subsequent calculations were done on standardized deviates so that all variances equalled unity. The calculated regression coefficients were decoded back to conform with the original scale of measurement. The

variance differences were consistent for males and females treated together as well as separately.

As explained in the materials and methods section, derivation of measured regression coefficients requires first a rough estimate of product moment correlation coefficients. Values were calculated for all thresholds with the sexes pooled (Appendix - A19). The value of r = 0.36 for the threshold nearest the mean is very close to the overall sib-sib correlation (i.e., r = 0.42). However, as the threshold moves away from the mean on either side, the coefficients decrease very rapidly to essentially zero. Recalling that birthweight increases with birth order, for thresholds near the mean a proband has greatest probability of being of an intermediate birth order and deviations of his sibling's birthweights will be partly due to birth order effects such that differences for sibs of lower birth order will partly balance out differences for sibs of higher birth order. As the threshold moves away from the mean, the probability that the proband has a more extreme birthweight increases so that the sibs are more likely to be of either higher or lower (i.e., if threshold is below or above the mean respectively) birth order but not both. As a result, the balancing of deviations due to birth order effects decreases and causes a decrease in correlation. The confounding parity effects account to some extent then for the pattern of decreasing correlations as the threshold moves away from the mean. Since extreme birthweights are more likely to be non-heritable effects due to environmental causes, it is also expected that the non-genetic variation becomes greater at the tails. This effect is,

however, probably of minor importance compared to the parity confounding effects. Finally, from the Law of Large Numbers, we know that as sample size increases the deviation of the estimated coefficient from the real coefficient (i.e., the overall coefficient) is expected to decrease. The combination of the parity effects with the sampling variations lead us to expect the observed trend of the correlation coefficients.

Falconer (1965) gave the equation $b = (X_g - X_r)/a_g$ for the regression coefficient of relatives on propositi as well as the formula for the sampling variance of the estimate. Using this formula, estimates of regression coefficients and their variances were obtained separately by sex and threshold for the simulated quasi-continuous traits in order to compare these with measured coefficients. Such derivations are of course independent of the scale of measurement since the threshold is a function of the scale. According to the assumptions of the model, however, comparison can be expected to be good only for calculated coefficients which are measured on a scale corresponding to a Gaussian frequency distribution of the underlying variate.

The coefficients derived from Falconer's equation as well as their sampling variances are given in the Appendix (A20). The regressions nearest the mean are lowest, increasing as the threshold moves away but reaching a plateau value near 0.3 at about six thresholds below the mean and strictly increasing to a value of approximately 0.5 around seven thresholds above the mean. The plateau for thresholds below the mean likely

reflects the negative skewness of the frequency distribution while the fact that the highest coefficients are found at thresholds furthest above the mean are most probably due to the slight deficiency of higher birthweights. The overall trend is then as expected. Breakdown by sex gives generally higher values than the pooled data except for the threshold nearest the mean. This too is as expected.

Measured regression coefficients and their sampling variances were obtained with weighting by both sibship size and correlation for the five different scales of measurement described earlier. This was done for sexes pooled and separately and also separately by threshold (Appendix - A21, A22 and A23). No quantifiable relationship could be discerned between the measured regression values and the degree of departure of the corresponding distribution from normality. Qualitatively it is seen that the measured coefficients are nearest the derived coefficients at threshold values where there are the smallest departures from normality. As examples, the empirical transformation, (d), gives a bad fit to normality at both ends of the distribution but a much better approximation to normality than the untransformed data for values below the mean. The log transformation gives an intermediate fit for values below the mean with little change for values greater than the mean. These departures from normality are exactly paralleled in the nearness of measured coeficients to the derived coefficients for all five scales of measurement. Unfortunately, however, the distributions for all five scales are significantly different from normality and even at the best points, differences between measured and

derived coefficients are too great to allow anything other than the qualitative conclusion that in all cases the bad fit of derived coefficients is a reflection of the non-normality of the corresponding frequency distributions. For the range of incidences of about .01 or less (which is the approximate range for human traits thought to be quasi-continuous) the percentage deviation of the derived coefficients from observed coefficient (measured from untransformed data) is about 20 to 25 percent for thresholds above the mean and greater than this for thresholds below the mean because of the negative skewness of the distribution of birthweights. Thus, it was not possible to carry out a critical test of Falconer's theorem. Treating the data separately by sex made no difference to the results.

The necessity of normality of the distribution of the underlying variate poses an interesting question as to the applicability of Falconer's theorem to biological data. Falconer's unit of measurement is the standardized normal deviate so that in practice a quasi-continuous trait with an abrupt threshold may give rise to a proportion of affected individuals who do or do not lie beyond the threshold when the scale of measurement is absolute but who respectively do not or do lie beyond this point when the scale is changed and measurements are in terms of standardized normal deviates. That is, there need not be a one to one point correspondence that maintains the same order of dichotomization with respect to the threshold between the biological scale of measurement and the percentile scale of measurement used to develop the theory. Since we have seen that the

theorem is very sensitive to departures from normality and since it is unlikely that any biological data have substantially more normal distributions than do these birthweights, the usefulness of Falconer's theorem for the prediction of either risks to relatives or derivation of heritability estimates becomes extremely questionable.

The major conclusion of this study is that researchers who utilize quasi-continuous models ought to do so very critically. A thorough search for major gene effects ought first to be carried out. A combined use of segregation and regression analyses ought to be the first step and when one resorts to quasi-continuous models, expanded models with non-abrupt thresholds should be utilized. This may perhaps help to prevent a general inclusion of unresolved traits in the category of quasi-continuous variations. This is especially important for data which are to be used for genetic counselling purposes.

We have seen that the original models as derived by Edwards (1960) and Falconer (1965) are not reliable predictors. The first step in improving the models has already been taken by Edwards (1967) and Morton and his co-workers (Campbell, 1969) by assuming a non-abrupt threshold. Since the sigmoid curve seems to be the most reasonable function to describe the threshold (Campbell, 1969), it is desirable that this function be utilized and its consequences determined despite the mathematical difficulties involved. Nevertheless, the extension derived by Campbell, Elston and Morton (see Campbell, 1969) in assuming a truncate normal distribution of risk is a welcome improvement as evidenced by the results of

their simulation study using fingerprint data. A further much needed improvement is a reliable test for the additivity of gene effects. Hopefully, a combination of these improvements will give us some indications of the biological mechanisms determining many unresolved traits as well as providing us with more realistic means of calculating risks to relatives of probands.

SUMMARY

A large body of human birthweight data was used to simulate quasi-continuous traits with abrupt thresholds by imposing arbitrary thresholds on the birthweight distribution and thereby simulating the quasi-continuous trait, "extreme birthweight". The simulation was used to test Edwards' (1960) prediction that the sib risk for such traits is about equal to the square root of the population incidence of the trait and also to test Falconer's theorem (1965) that the regression of relatives on propositi, with respect to the underlying variate, can be determined from the population incidence and the risk to sibs. Birthweight served as the measure of the underlying variate.

Edwards' prediction gave a poor fit to observed frequencies which it generally overestimates by about twenty percent. This is partly attributed to the low heritability of birthweight. No critical test of Falconer's theorem could be made because no transformation was found to normalize the frequency distribution of birthweight. His method is highly sensitive to departures from normality.

The practical value of the models and resulting theory were briefly discussed and it was concluded that they are likely to be inapplicable to real biological situations.

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APPENDIX OF TABLES

a) Parameters of Birthweight Distributions

i) Males and Females

Birth order	Sample size	Mean (grams)	Standard Deviation (grams)	Skewness	Kurtosis	Kolmogorov-Smirnov Statistic
All	412100	3354.4	549.5	-.483	1.879	.0402
1	120942	3273.4	525.6	-.594	2.047	.0442
2	111690	3357.2	533.1	-.492	1.871	.0392
3	81316	3392.5	543.4	-.453	1.880	.0366
4	46846	3412.3	562.3	-.487	1.866	.0384
5	23420	3417.6	586.8	-.459	1.627	.0378
6	11887	3424.1	606.0	-.503	1.803	.0426
7	6591	3433.8	620.8	-.511	1.600	.0382
8	3750	3436.9	641.9	-.463	1.550	.0399
9	2201	3434.7	661.0	-.636	1.862	.0477
> 9	3457	3456.1	697.0	-.651	2.108	.0508

a) Parameters of Birthweight Distributions

ii) Males only

Birth Order	Sample size	Mean (grams)	Standard Deviation (grams)	Skewness	Kurtosis	Kolmogorov-Smirnov Statistic
All	210950	3417.2	561.6	-.533	1.941	.0414
1	62188	3328.2	537.5	-.629	2.058	.0471
2	57142	3423.9	543.3	-.536	1.880	.0399
3	41703	3461.1	553.5	-.501	1.961	.0353
4	23809	3476.3	576.1	-.549	1.943	.0402
5	11925	3483.0	596.3	-.563	1.756	.0394
6	5994	3486.9	627.9	-.588	1.864	.0417
7	3402	3493.8	627.9	-.583	1.787	.0385
8	1951	3513.5	662.3	-.564	1.663	.0516
9	1092	3492.0	672.9	-.698	2.103	.0530
> 9	1744	3526.4	725.9	-.651	2.103	.0530

a) Parameters of Birthweight Distributions

iii) Females only

Birth Order	Sample size	Mean (grams)	Standard Deviation (grams)	Skewness	Kurtosis	Kolmogorov -Smirnov Statistic
All	201150	3288. 5	528. 6	-. 490	2. 001	. 0398
1	58754	3215. 5	506. 3	-. 614	2. 168	. 0423
2	54548	3287. 3	513. 1	-. 513	2. 037	. 0394
3	39613	3320. 3	522. 8	-. 468	1. 958	. 0385
4	23037	3346. 1	539. 7	-. 487	1. 923	. 0371
5	11495	3349. 8	568. 9	-. 390	1. 666	.0366
6	5893	3360. 3	573. 8	-. 470	1. 856	. 0439
7	3189	3369. 8	606. 8	-. 465	1. 514	. 0391
8	1799	3353. 7	608. 4	-. 420	1. 600	.0431
9	1109	3378. 4	644. 4	-. 607	1. 917	. 0468
>9	1713	3384. 6	658. 8	-. 714	2. 175	. 0520

b) Family Size Distribution

Mean family size = 1.869

Variance in family size = 1.2686

Family size	Number of families
1	109079
2	61409
3	30539
4	12545
5	4472
6	1549
7	616
8	175
9	68
10	20
11	6
12	5
13	1
> 13	5
Total	220489

Thresholds

Probands and Sibs of Both Sexes			Male Probands and Sibs			Female Probands and Sibs		
Threshold	Distance * from $\bar{x}$	Frequency of trait	Threshold	Distance * from $\bar{x}$	Frequency of trait	Threshold	Distance * from $\bar{x}$	Frequency of trait
1	-4.53	.0009	1	-4.97	.0009	1	-5.04	.0009
2	-4.12	.0024	2	-4.53	.0023	2	-4.57	.0024
3	-3.70	.0042	3	-4.08	.0043	3	-4.09	.0042
4	-3.29	.0065	4	-3.64	.0065	4	-3.62	.0065
5	-2.87	.0100	5	-3.19	.0099	5	-3.15	.0101
6	-2.46	.0163	6	-2.75	.0160	6	-2.67	.0166
7	-2.04	.0272	7	-2.30	.0261	7	-2.20	.0284
8	-1.63	.0539	8	-1.86	.0495	8	-1.72	.0584
9	-1.21	.1127	9	-1.41	.0982	9	-1.25	.1280
10	-0.80	.2193	10	-0.96	.1873	10	-0.78	.2528
11	-0.39	.3987	11	-0.52	.3480	11	-0.31	.4520
12	+0.03	.6012	12	-0.07	.6520	12	+0.16	.5480
13	+0.44	.3921	13	+0.37	.4474	13	+0.64	.3341
14	+0.86	.2132	14	+0.81	.2571	14	+1.11	.1671
15	+1.27	.0984	15	+1.26	.1251	15	+1.58	.0705
16	+1.69	.0433	16	+1.71	.0572	16	+2.05	.0288
17	+2.10	.0152	17	+2.15	.0209	17	+2.53	.0093
18	+2.52	.0051	18	+2.60	.0071	18	+3.00	.0031
19	+2.93	.0016	19	+3.04	.0021	19	+3.47	.0010
20	+3.34	.0005	20	+3.49	.0007	20	+3.95	.0004
21	+3.76	.0002	21	+3.93	.0002	21	+4.42	.0001
22	+4.17	.0001	22	+4.38	.0001	22	+4.89	.00003
23	+4.59	.00003	23	+4.82	.00004	23	+5.36	.00002
24	+5.00	.00001	24	+5.27	.00001	24	+5.84	.00000

* in units of standard deviations.

Thresholds

Probands and Sibs of Both Sexes			Male Probands and Sibs			Female Probands and Sibs		
Threshold	Distance * from $\bar{x}$	Frequency of trait	Threshold	Distance * from $\bar{x}$	Frequency of trait	Threshold	Distance * from $\bar{x}$	Frequency of trait
1	-4.53	.0009	1	-4.97	.0009	1	-5.04	.0009
2	-4.12	.0024	2	-4.53	.0023	2	-4.57	.0024
3	-3.70	.0042	3	-4.08	.0043	3	-4.09	.0042
4	-3.29	.0065	4	-3.64	.0065	4	-3.62	.0065
5	-2.87	.0100	5	-3.19	.0099	5	-3.15	.0101
6	-2.46	.0163	6	-2.75	.0160	6	-2.67	.0166
7	-2.04	.0272	7	-2.30	.0261	7	-2.20	.0284
8	-1.63	.0539	8	-1.86	.0495	8	-1.72	.0584
9	-1.21	.1127	9	-1.41	.0982	9	-1.25	.1280
10	-0.80	.2193	10	-0.96	.1873	10	-0.78	.2528
11	-0.39	.3987	11	-0.52	.3480	11	-0.31	.4520
12	+0.03	.6012	12	-0.07	.6520	12	+0.16	.5480
13	+0.44	.3921	13	+0.37	.4474	13	+0.64	.3341
14	+0.86	.2132	14	+0.81	.2571	14	+1.11	.1671
15	+1.27	.0984	15	+1.26	.1251	15	+1.58	.0705
16	+1.69	.0433	16	+1.71	.0572	16	+2.05	.0288
17	+2.10	.0152	17	+2.15	.0209	17	+2.53	.0093
18	+2.52	.0051	18	+2.60	.0071	18	+3.00	.0031
19	+2.93	.0016	19	+3.04	.0021	19	+3.47	.0010
20	+3.34	.0005	20	+3.49	.0007	20	+3.95	.0004
21	+3.76	.0002	21	+3.93	.0002	21	+4.42	.0001
22	+4.17	.0001	22	+4.38	.0001	22	+4.89	.00003
23	+4.59	.00003	23	+4.82	.00004	23	+5.36	.00002
24	+5.00	.00001	24	+5.27	.00001	24	+5.84	.00000

* in units of standard deviations.

b) Males only

i) Thresholds below the mean:

Edwards' Predicted Risks				Observed Risks		
Threshold	Ascertained through last born	Complete Ascertainment	Ascertained through first born	Ascertained through last born	Complete Ascertainment	Ascertained through first born
1	.0313	.0293	.0307	.0392	.0268	.0444
2	.0498	.0484	.0504	.0375	.0335	.0352
3	.0669	.0654	.0678	.0303	.0362	.0517
4	.0824	.0805	.0833	.0471	.0476	.0384
5	.1012	.0996	.1043	.0708	.0733	.0618
6	.1286	.1267	.1324	.0728	.0668	.0580
7	.1647	.1615	.1694	.1304	.1230	.1060
8	.2255	.2225	.2344	.1848	.1786	.1508
9	.3167	.3133	.3282	.2675	.2690	.2420
10	.4352	.4328	.4520	.3726	.3388	.3109
11	.5889	.5899	.6118	.5095	.4721	.4320

ii) Thresholds above the mean:

Edwards' Predicted Risks				Observed Risks		
Threshold	Ascertained through last born	Complete Ascertainment	Ascertained through first born	Ascertained through last born	Complete Ascertainment	Ascertained through first born
12	.8082	.8075	.7910	.6237	.6544	.6949
13	.6707	.6689	.6454	.4921	.5397	.5873
14	.5113	.5071	.4808	.3816	.4199	.4693
15	.3588	.3537	.3292	.2602	.3104	.3652
16	.2462	.2391	.2179	.2049	.2296	.2761
17	.1503	.1444	.1261	.1262	.1540	.1730
18	.0877	.0840	.0732	.1233	.1382	.1933
19	.0485	.0463	.0397	.0192	.0674	.1632
20	.0262	.0257	.0210	.0731	.1023	---

Risks from different methods of ascertainment

c) Females only

i) Thresholds below the mean:

Threshold	Edwards' Predicted Risks			Observed Risks		
	Ascertained through last born	Complete Ascertainment	Ascertained through first born	Ascertained through last born	Complete Ascertainment	Ascertained through first born
1	.0325	.0303	.0316	.0476	.0307	---
2	.0515	.0493	.0529	.0166	.0438	.0689
3	.0667	.0644	.0680	.0422	.0357	.0659
4	.0832	.0807	.0843	.0285	.0443	.0485
5	.1032	.1044	.1051	.0700	.0802	.0223
6	.1332	.1288	.1354	.1166	.0889	.0798
7	.1722	.1686	.1772	.1463	.1430	.1503
8	.2458	.2418	.2530	.1991	.1976	.1710
9	.3616	.3577	.3729	.3266	.2972	.2715
10	.5041	.5028	.5220	.4429	.4059	.3654
11	.6713	.6723	.6918	.5834	.5400	.4885

ii) Thresholds above the mean:

Threshold	Edwards' Predicted Risk			Observed Risk		
	Ascertained through last born	Complete Ascertainment	Ascertained through first born	Ascertained through last born	Complete Ascertainment	Ascertained through first born
12	.7412	.7403	.7221	.5587	.6047	.6489
13	.5812	.5780	.5552	.4223	.4763	.5226
14	.4142	.4037	.3830	.3143	.3597	.4267
15	.2722	.2656	.2451	.2033	.2479	.3006
16	.1760	.1696	.1543	.1450	.1800	.2169
17	.1017	.0964	.0857	.0599	.1206	.1735
18	.0603	.0555	.0486	.0448	.0815	.0862
19	.0344	.0318	.0255	.0800	.0769	---
20	.0209	.0196	.0150	---	.0727	---

Edwards' Predictions

a) Complete Ascertainment: i) males and females

No. = Number
% Dev'n = Percentage deviation
X^2 = Chi-square value

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0009	.0300	10	8	551	.50	-50.00	4.1196
2	.0024	.0489	47	27	970	.57	-42.55	8.9440
3	.0042	.0648	75	47	1167	.63	-37.33	11.1713
4	.0065	.0806	114	59	1420	.52	-48.25	28.8513
5	.0100	.1000	214	141	2145	.66	-34.11	27.6616
6	.0163	.1276	468	287	3669	.61	-38.68	80.2368
7	.0272	.1649	1074	823	6512	.77	-23.37	70.2455
8	.0539	.2321	3711	2937	15991	.79	-20.86	210.2172
9	.1127	.3357	11960	9762	35626	.82	-18.38	608.0880
10	.2193	.4682	30477	23926	65081	.78	-21.49	2648.3227
11	.3987	.6314	70351	55624	111413	.79	-20.93	8364.7712
12	.6012	.7753	102629	83076	132354	.81	-19.05	16587.1553
13	.3921	.6261	72772	58788	116211	.81	-19.22	7188.9579
14	.2132	.4607	35478	29521	76843	.83	-16.79	1858.0926
15	.0984	.3136	11842	10323	37741	.87	-12.83	283.9363
16	.0433	.2080	4015	3948	19294	.98	- 1.67	1.4119
17	.0152	.1232	878	960	7124	1.09	+ 9.34	8.7348
18	.0051	.0714	180	270	2527	1.50	+50.00	48.4512
19	.0016	.0400	28	61	725	2.18	+117.86	40.4553
20	.0005	.0223	8	33	362	4.12	+312.60	79.8905
21	.0002	.0141	0	2	63	--	--	2.0160
22	.0001	.0100	0	0	31	--	--	--
23	.00003	.0055	0	0	26	--	--	--
24	.00001	.0032	0	0	6	--	--	--

Edwards' Predictions

a) Complete Ascertainment: ii) males only

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0009	.0293	4	4	149	1.00	0	0
2	.0023	.0484	12	9	268	.75	-25.00	.7852
3	.0043	.0654	23	13	359	.56	-43.48	4.6454
4	.0065	.0805	28	17	357	.61	-39.29	4.6892
5	.0099	.0996	55	41	559	.74	-25.45	3.9525
6	.0160	.1267	123	65	973	.53	-47.15	31.3072
7	.0261	.1615	254	194	1576	.76	-23.62	16.8964
8	.0495	.2225	825	663	3712	.80	-19.64	40.9013
9	.0981	.3133	2423	2081	7736	.86	-14.11	70.2871
10	.1873	.4328	6195	4851	14315	.78	-21.69	514.0348
11	.3480	.5899	15458	12373	26205	.80	-19.96	1501.2532
12	.7515	.8075	27137	21996	33608	.81	-18.94	5058.3007
13	.4474	.6689	21479	17331	32112	.81	-19.31	2419.2179
14	.2571	.5071	11617	9621	22911	.83	-17.18	695.7022
15	.1251	.3537	4255	3735	12031	.88	-12.22	98.3224
16	.0572	.2391	1532	1472	6409	.96	- 3.92	3.0880
17	.0209	.1444	351	375	2434	1.07	+ 6.84	1.9175
18	.0071	.0840	79	130	940	1.65	+64.56	35.9450
19	.0021	.0463	11	17	252	1.55	+54.55	3.4221
20	.0007	.0267	3	13	127	4.33	+333.33	23.7987
21	.0002	.0143	0	0	18	--	--	--
22	.0001	.0097	0	0	12	--	--	--
23	.00004	.0062	0	0	13	--	--	--
24	.00001	.0038	0	0	2	--	--	--

Edwards' Predictions

a) Complete Ascertainment: iii) females only

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0009	.0303	3	4	130	1.33	+33.33	0.3412
2	.0024	.0493	11	10	228	.91	- 9.09	0.0955
3	.0041	.0644	16	9	252	.56	-43.75	3.2701
4	.0065	.0807	27	15	338	.55	-44.44	5.7964
5	.0101	.1004	51	41	511	.80	-19.61	2.1782
6	.0166	.1288	108	75	843	.69	-30.56	11.5650
7	.0284	.1686	280	238	1664	.85	-15.00	7.5746
8	.0584	.2418	1040	851	4306	.82	-18.17	45.2843
9	.1280	.3577	3601	2993	10069	.83	-16.88	159.8087
10	.2528	.5028	9076	7327	18051	.81	-19.27	677.8786
11	.4520	.6723	19785	15894	29430	.80	-19.67	2334.9331
12	.5480	.7403	23997	19602	32416	.82	-18.31	3099.2722
13	.3341	.5780	15036	12392	26013	.82	-17.58	1101.7863
14	.1671	.4087	6445	5674	15771	.88	-11.96	155.9731
15	.0705	.2656	1835	1713	6910	.93	- 6.65	11.0440
16	.0288	.1696	549	584	3243	1.06	+ 6.38	2.6860
17	.0093	.0964	106	133	1102	1.25	+25.47	7.6093
18	.0031	.0555	18	20	325	1.10	+11.11	0.2353
19	.0010	.0318	3	8	104	2.67	+166.67	4.7306
20	.0004	.0196	1	4	55	4.00	+300.00	2.7429
21	.0001	.0107	0	0	11	--	--	--
22	.00003	.0055	0	0	3	--	--	--
23	.00001	.0039	0	0	3	--	--	--
24	.000005	.0022	0	0	0	--	--	--

Edwards' Predictions

b) Ascertainment through the first born child only and risk to later born children - i) males and females

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0010	.0312	4	2	152	.50	-50.00	1.0270
2	.0027	.0516	16	12	325	.75	-25.00	1.0518
3	.0046	.0678	25	19	369	.76	-24.00	1.5447
4	.0070	.0838	35	16	420	.46	-54.29	11.2519
5	.0110	.1047	75	33	921	.44	-56.00	26.2507
6	.0179	.1339	153	73	1146	.48	-52.29	48.2752
7	.0300	.1743	371	244	2147	.66	-34.23	52.5560
8	.0594	.2436	1304	845	5356	.65	-35.20	213.5595
9	.1230	.3507	4152	2927	11842	.71	-29.50	556.5620
10	.2375	.4873	10747	7352	22054	.68	-31.59	2091.8584
11	.4250	.6520	23770	16445	36460	.69	-30.82	6485.4650
12	.5750	.7538	31061	27345	40964	.88	-11.96	1838.9569
13	.3638	.6023	20503	18776	33993	.92	- 8.42	366.5598
14	.1901	.4360	8722	8791	20008	1.01	+ 0.79	0.9677
15	.0849	.2913	2695	3015	9254	1.12	+11.87	53.6084
16	.0360	.1896	811	1063	4279	1.31	+31.07	96.6147
17	.0120	.1095	156	236	1430	1.51	+51.28	46.0492
18	.0039	.0625	31	79	502	2.55	+154.84	79.2143
19	.0011	.0335	4	14	134	3.50	+250.00	25.7692
20	.0003	.0183	0	1	38	--	--	0
21	.0001	.0106	0	0	6	--	--	--
22	.00004	.0064	0	0	7	--	--	--
23	.00001	.0037	0	0	1	--	--	--
24	.00001	.0030	0	0	3	--	--	--

Edwards' Predictions

b) Ascertainment through the first born child only and risk to later born children - ii) males only.

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0009	.0307	1	2	45	2.00	+100.00	0
2	.0025	.0504	4	3	85	.75	- 25.00	0
3	.0046	.0676	7	6	116	.86	- 14.29	0
4	.0069	.0833	8	4	104	.50	- 50.00	1.2932
5	.0109	.1043	20	12	194	.60	- 40.00	2.7936
6	.0175	.1324	38	17	293	.45	- 55.26	13.3347
7	.0287	.1694	81	51	481	.63	- 37.04	13.3611
8	.0550	.2344	293	189	1253	.64	- 35.49	48.1813
9	.1077	.3282	829	612	2528	.74	- 26.18	84.5179
10	.2043	.4520	2218	1526	4908	.69	- 31.20	393.9154
11	.3743	.6118	5349	3778	8744	.71	- 29.37	1188.3858
12	.6257	.7910	8352	7338	10559	.88	- 12.14	588.9872
13	.4165	.6454	6104	5555	9458	.91	- 8.99	139.2408
14	.2312	.4808	2947	2877	6130	.98	- 2.38	3.2021
15	.1084	.3292	1031	1144	3132	1.11	+ 10.96	18.4626
16	.0475	.2179	321	407	1474	1.27	+ 26.79	29.4551
17	.0164	.1281	63	86	497	1.36	+ 36.51	9.6157
18	.0054	.0732	13	35	181	2.69	+169.23	35.2994
19	.0016	.0397	1	8	49	8.00	+700.00	24.7578
20	.0004	.0210	0	0	15	--	--	--
21	.0001	.0119	0	0	1	--	--	--
22	.0001	.0084	0	0	3	--	--	--
23	.00003	.0051	0	0	1	--	--	--
24	.00002	.0042	0	0	2	--	--	--

Edwards' Predictions

b) Ascertainment through the first born child only and risk to later born children - iii) females only

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0010	.0316	1	0	40	0	-100.00	0
2	.0028	.0529	4	6	87	1.50	+ 50.00	0.2343
3	.0046	.0680	6	6	91	1.00	0	0
4	.0071	.0843	8	5	103	.62	- 37.50	0.5751
5	.0110	.1051	14	3	134	.21	- 78.57	8.2372
6	.0183	.1354	35	21	263	.60	- 40.00	6.4596
7	.0314	.1772	97	83	552	.86	- 14.43	2.4514
8	.0640	.2530	357	242	1415	.68	- 32.21	49.5448
9	.1390	.3729	1237	902	3320	.73	- 27.08	144.6001
10	.2725	.5220	3141	2199	6018	.70	- 29.99	590.9438
11	.4785	.6918	6516	4603	9421	.71	- 29.36	1821.3765
12	.5215	.7221	7135	6412	9881	.90	- 10.13	263.6228
13	.3082	.5552	4190	3945	7548	.94	- 5.85	32.2010
14	.1467	.3830	1524	1707	3981	1.12	+ 12.01	35.6044
15	.0601	.2451	382	469	1560	1.23	+ 22.77	26.2394
16	.0238	.1543	107	151	696	1.41	+ 41.12	21.3804
17	.0073	.0857	18	38	219	2.11	+111.11	24.2123
18	.0024	.0486	2	5	58	2.50	+150.00	1.6720
19	.0007	.0255	0	0	11	--	--	--
20	.0002	.0150	0	0	5	--	--	--
21	.0001	.0092	0	0	0	--	--	--
22	.00001	.0031	0	0	0	--	--	--
23	0	0	0	0	0	--	--	--
24	0	0	0	0	0	--	--	--

Edwards' Predictions

c) Ascertainment through the last born child only and risk to earlier born children - i) males and females

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Devn from Expected	X^2
1	.0010	.0319	5	4	183	.80	-20.00	0
2	.0026	.0506	13	6	273	.46	-53.85	3.9577
3	.0045	.0668	21	12	326	.57	-42.86	4.1227
4	.0069	.0828	35	15	424	.43	-57.14	12.4568
5	.0104	.1022	55	39	548	.71	-29.09	5.1738
6	.0171	.1309	129	80	991	.62	-37.98	21.3978
7	.0284	.1684	298	239	1774	.80	-19.80	14.0396
8	.0555	.2357	1064	874	4515	.82	-17.86	44.3893
9	.1152	.3394	3457	3056	10187	.88	-11.60	70.4078
10	.2211	.4702	8494	7252	18064	.85	-14.62	342.7938
11	.3977	.6306	19740	16849	31304	.85	-14.65	1146.1482
12	.6023	.7761	30374	23068	39137	.76	-24.05	7848.5977
13	.3950	.6285	22275	16329	35442	.73	-26.69	4272.3171
14	.2174	.4663	11480	8380	24621	.73	-27.00	1568.4070
15	.1020	.3193	4074	2892	12760	.71	-29.01	503.7845
16	.0461	.2147	1472	1176	6860	.80	-20.11	75.7831
17	.0166	.1288	342	271	2661	.79	-20.76	16.9135
18	.0057	.0755	79	91	1055	1.15	+15.19	1.9703
19	.0018	.0422	13	18	311	1.38	+38.46	2.0070
20	.0006	.0237	2	6	117	3.00	+200.00	3.6786
21	.0002	.0130	0	1	25	--	--	0
22	.0001	.0082	0	0	7	--	--	--
23	.00004	.0060	0	0	23	--	--	--
24	.00001	.0037	0	0	3	--	--	--

Edwards' Predictions

c) Ascertainment through the last born child only and risk to earlier born children - ii) males only

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0010	.0313	1	2	51	2.00	+100.00	0
2	.0025	.0498	3	3	80	1.00	0	0
3	.0045	.0669	6	3	99	.50	- 50.00	0.7699
4	.0068	.0824	8	5	106	.62	- 37.50	0.5739
5	.0102	.1012	12	9	127	.75	- 25.00	0.3824
6	.0165	.1286	31	18	247	.58	- 41.94	6.2340
7	.0271	.1647	71	57	437	.80	- 19.72	3.2961
8	.0509	.2255	235	193	1044	.82	- 17.87	9.6869
9	.1003	.3167	710	645	2243	.91	- 9.15	8.7067
10	.1894	.4352	1723	1476	3961	.86	- 14.34	62.6691
11	.3468	.5889	4234	3664	7190	.86	- 13.46	186.6840
12	.6532	.8082	7858	6065	9724	.77	- 22.82	2131.9738
13	.4499	.6707	6388	4687	9524	.73	- 26.63	1375.5838
14	.2615	.5113	3617	2700	7075	.75	- 25.35	475.6545
15	.1287	.3588	1408	1022	3927	.73	- 27.41	164.9699
16	.0606	.2462	556	463	2259	.83	- 16.73	20.6344
17	.0226	.1503	130	110	871	.85	- 15.38	3.6167
18	.0077	.0877	33	47	381	1.42	+ 42.42	6.5026
19	.0023	.0485	5	2	104	.40	- 60.00	0.9290
20	.0007	.0262	1	3	41	3.00	+200.00	0.6919
21	.0002	.0126	0	0	4	--	--	--
22	.0001	.0094	0	0	4	--	--	--
23	.00004	.0067	0	0	11	--	--	--
24	.00002	.0042	0	0	0	--	--	--

Edwards' Predictions

c) Ascertainment through the last born child only and risk to earlier born children - iii) females only

Threshold	Incidence	Edwards' Prediction	Expected No. of Affected Sibs	Observed No. of Affected Sibs	Total No. of Sibs	Observed / Expected	% Dev'n from Expected	X^2
1	.0011	.0325	1	2	42	2.00	+100.00	0
2	.0026	.0515	3	1	60	.33	- 66.67	0.4173
3	.0044	.0667	4	3	71	.75	- 25.00	0
4	.0069	.0832	8	3	105	.37	- 62.50	2.2974
5	.0106	.1032	16	11	157	.69	- 31.25	1.1452
6	.0177	.1332	31	28	240	.90	- 9.68	0.3334
7	.0296	.1722	76	65	444	.85	- 14.47	1.9209
8	.0604	.2458	304	247	1240	.81	- 18.75	14.1587
9	.1307	.3616	1028	929	2844	.90	- 9.63	14.9311
10	.2541	.5041	2468	2169	4897	.88	- 12.12	73.0297
11	.4506	.6713	5456	4742	8128	.87	- 13.09	284.2296
12	.5494	.7412	7067	5328	9536	.75	- 24.61	1652.7578
13	.3378	.5812	4649	3378	7999	.73	- 27.34	829.7026
14	.1716	.4142	2135	1621	5156	.76	- 24.07	211.1984
15	.0741	.2722	663	496	2439	.75	- 25.19	57.7681
16	.0310	.1760	202	168	1150	.83	- 16.83	6.9422
17	.0103	.1017	42	25	417	.60	- 40.48	7.6516
18	.0036	.0603	9	7	156	.78	- 22.22	0.1243
19	.0012	.0344	1	3	50	3.00	+200.00	0.6872
20	.0004	.0209	0	0	20	--	--	--
21	.0002	.0133	0	0	9	--	--	--
22	.00005	.0068	0	0	1	--	--	--
23	.00003	.0053	0	0	3	--	--	--
24	.00001	.0030	0	0	0	--	--	--

Data Transformations to and from Normality -

(x = birthweight code)

	Transformation	Skewness	Kurtosis	Kolmogorov - Smirnov Statistic
1	$\log_{10}(x + 1)$	-2.3465	+13.9658	.0885
2	$\sqrt{x + 0.5}$	-1.2380	+ 5.2603	.0615
3	none	-0.4835	+ 1.8989	.0402
4	'empirical'	-0.1319	- 0.0386	.0179
5	$.86(1+.15(x-12)^2)_c^{-.044(x-12)^2}$	+0.2799	+ 0.5055	1.0000

Product Moment Correlation Coefficients

(proband vs mean of sibs - both sexes used)

Threshold	Correlation Coefficient	Sample Size
2	- .00939	639
3	- .03464	1154
4	+ .00315	1793
5	- .00273	2764
6	- .02581	4492
7	- .03751	7542
8	- .00407	15127
9	+ .05276	32198
10	+ .13504	63590
11	+ .22073	117362
12	+ .36450	185659
13	+ .31343	122183
14	+ .26714	66966
15	+ .23681	31130
16	+ .19866	13698
17	+ .16592	4873
18	+ .11366	1662
19	+ .03489	516
20	- .00361	183

Regression Coefficients - complete ascertainment

(derived from incidence and observed risks by means of Falconer's equation).

Threshold	Males and Females		Males		Females	
	b	V(b) $\times 10^{-4}$	b	V(b) $\times 10^{-4}$	b	V(b) $\times 10^{-4}$
2	.2916	7.0923	.3183	22.1417	.3574	22.0774
3	.3003	5.1065	.2821	17.8635	.2861	15.5234
4	.2653	2.5020	.2917	16.5167	.2771	18.1151
5	.3076	2.4925	.3282	8.8530	.3448	9.2166
6	.2877	1.4962	.2578	6.1562	.3146	6.0250
7	.3382	0.7525	.3371	3.0882	.3678	2.7699
8	.3482	0.3348	.3554	1.3768	.3615	1.2179
9	.3525	0.1837	.3853	0.7796	.3743	0.6766
10	.3268	0.1466	.3319	0.5994	.3509	0.5885
11	.2619	0.1794	.2930	0.5778	.2568	0.7604
12	.1232	0.3802	-.6881	3.8557	-1.9135	122.8355
13	.3089	0.1617	.2568	0.6999	.3555	0.5472
14	.3651	0.1231	.3534	0.4768	.4059	0.4881
15	.3852	0.1609	.3971	0.5469	.4153	0.7638
16	.4202	0.2432	.4190	0.7652	.4301	1.2933
17	.4214	0.5639	.4224	1.6711	.4398	3.3405
18	.4594	1.3576	.4905	3.3998	.3944	13.1465
19	.4962	4.2977	.4322	14.7594	.4942	29.0317
20	.5503	85.1723	.5557	18.9849	.5256	49.4415

Measured Regression Coefficients for Comparison to Falconer's Derived Coefficient

a) males and females - complete ascertainment

Threshold	Transformation 1		Transformation 2		Transformation 3		Transformation 4		Transformation 5	
	b	$V(b) \times 10^{-4}$	b	$V(b) \times 10^{-4}$	b	$V(b) \times 10^{-4}$	b	$V(b) \times 10^{-4}$	b	$V(b) \times 10^{-4}$
2	2.1632	0.6281	2.0605	0.6335	5.2164	13.1630	2.1331	1.9790	6.0987	11.3277
3	1.8617	0.3167	1.8502	0.2737	3.8874	4.8907	2.0497	0.7485	3.8165	5.4667
4	1.6656	0.1978	1.6954	0.1744	3.0958	2.4737	2.0194	0.4813	2.4361	2.4190
5	1.4988	0.1071	1.5459	0.0998	2.4758	1.0824	1.9582	0.2696	1.6063	0.7710
6	1.3597	0.0478	1.4088	0.0479	2.0082	0.4002	1.8173	0.1413	1.1675	0.2015
7	1.2505	0.0196	1.2934	0.0210	1.6743	0.1394	1.6815	0.0681	0.9419	0.0553
8	1.1576	0.0068	1.1908	0.0078	1.4176	0.0419	1.4756	0.0300	0.8306	0.0145
9	1.0964	0.0022	1.1204	0.0026	1.2568	0.0121	1.3217	0.0112	0.8155	0.0044
10	1.0594	0.0008	1.0764	0.0010	1.1603	0.0042	1.2207	0.0046	0.8586	0.0021
11	1.0340	0.0003	1.0452	0.0004	1.0932	0.0017	1.1252	0.0020	0.9343	0.0016
12	0.9770	0.0001	0.9780	0.0001	0.9422	0.0003	0.9313	0.0004	0.9973	0.0008
13	0.9695	0.0001	0.9603	0.0001	0.9222	0.0005	0.9096	0.0006	0.9402	0.0016
14	0.9611	0.0002	0.9483	0.0002	0.8994	0.0009	0.8858	0.0010	0.8677	0.0014
15	0.9522	0.0003	0.9352	0.0005	0.8746	0.0017	0.8627	0.0018	0.8195	0.0026
16	0.9445	0.0007	0.9239	0.0011	0.8535	0.0035	0.8500	0.0039	0.8278	0.0077
17	0.9368	0.0017	0.9121	0.0029	0.8318	0.0095	0.8295	0.0101	0.9197	0.0339
18	0.9296	0.0048	0.9013	0.0082	0.8172	0.0265	0.8166	0.0282	1.1189	0.1733
19	0.9247	0.0147	0.8934	0.0252	0.7990	0.0785	0.8107	0.0842	1.5386	0.8444
20	0.9184	0.0477	0.8853	0.0750	0.7866	0.2200	0.8033	0.2307	2.0941	2.5320

Measured Regression Coefficients for Comparison to Falconer's Derived Coefficient

b) males only - complete ascertainment

Threshold	Transformation 1		Transformation 2		Transformation 3		Transformation 4		Transformation 5	
	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}
2	2.1672	2.7534	2.0709	2.7764	5.2957	56.9972	2.1868	8.1625	5.9530	52.8311
3	1.8712	1.0070	1.8667	0.9230	3.9639	16.4130	2.1127	2.7869	3.7080	16.9683
4	1.6876	0.6787	1.7206	0.6220	3.2009	8.9633	2.0809	1.8157	2.4313	8.1303
5	1.5162	0.3947	1.5658	0.3802	2.5402	4.2183	2.0052	1.0989	1.6041	2.6814
6	1.3770	0.8091	1.4294	0.1848	2.0664	1.5738	1.8713	0.5755	1.1578	0.7295
7	1.2682	0.0811	1.3145	0.0879	1.7275	0.5990	1.7347	0.2980	0.9375	0.2200
8	1.1730	0.0300	1.2091	0.0344	1.4576	0.1899	1.5207	0.1359	0.8297	0.0618
9	1.1074	0.0103	1.1338	0.0124	1.2843	0.0588	1.3558	0.0539	0.8133	0.0203
10	1.0672	0.0034	1.0861	0.0047	1.1796	0.0203	1.2457	0.0216	0.8538	0.0096
11	1.0385	0.0014	1.0509	0.0019	1.1046	0.0075	1.1399	0.0089	0.9335	0.0066
12	0.9789	0.0002	0.9733	0.0003	0.9472	0.0011	0.9379	0.0014	0.9916	0.0028
13	0.9722	0.0003	0.9639	0.0005	0.9295	0.0016	0.9186	0.0020	0.9424	0.0036
14	0.9646	0.0005	0.9530	0.0007	0.9085	0.0026	0.8967	0.0030	0.8776	0.0044
15	0.9569	0.0008	0.9416	0.0014	0.8867	0.0049	0.8764	0.0054	0.8335	0.0080
16	0.9494	0.0018	0.9304	0.0030	0.8658	0.0100	0.8633	0.0110	0.8417	0.0218
17	0.9424	0.0045	0.9196	0.0077	0.8456	0.0257	0.8442	0.0272	0.9352	0.0868
18	0.9342	0.0150	0.9077	0.0243	0.8248	0.0760	0.8290	0.0780	1.1164	0.4441
19	0.9293	0.0463	0.8996	0.0796	0.8102	0.2465	0.8218	0.2640	1.5490	2.5160
20	0.9273	0.1481	0.8966	0.2409	0.8061	0.6992	0.8225	0.7250	2.1032	8.5564

Measured Regression Coefficients for Comparison to Falconer's Derived Coefficient

c) females only - complete ascertainment

Threshold	Transformation 1		Transformation 2		Transformation 3		Transformation 4		Transformation 5	
	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}	b	V(b) x 10^{-4}
2	2.1289	3.1667	2.9263	3.0015	5.0605	59.9115	2.0674	8.8357	6.1203	58.0061
3	1.8451	1.4595	1.8291	1.2717	3.8063	21.7768	1.9904	3.5474	3.9041	25.3593
4	1.6440	0.8112	1.6704	0.7304	3.0024	9.9167	1.9605	2.1186	2.4358	10.0161
5	1.4778	0.4367	1.5214	0.4128	2.3982	4.2651	1.8977	1.1752	1.6177	3.1021
6	1.3394	0.2027	1.3839	0.2051	1.9363	1.6417	1.7476	0.6193	1.1868	0.8488
7	1.2296	0.0776	1.2681	0.0836	1.6092	0.5313	1.6142	0.2809	0.9527	0.2210
8	1.1408	0.0233	1.1704	0.0266	1.3710	0.1375	1.4222	0.1037	0.8355	0.0524
9	1.0843	0.0065	1.1054	0.0079	1.2246	0.0357	1.2819	0.0344	0.8224	0.0150
10	1.0510	0.0023	1.0656	0.0029	1.1376	0.0121	1.1910	0.0135	0.8655	0.0071
11	1.0283	0.0010	1.0377	0.0012	1.0774	0.0049	1.1049	0.0061	0.9359	0.0051
12	0.9764	0.0002	0.9700	0.0004	0.9406	0.0013	0.9288	0.0017	1.0056	0.0035
13	0.9684	0.0004	0.9590	0.0006	0.9196	0.0022	0.9061	0.0027	0.9419	0.0051
14	0.9602	0.0007	0.9471	0.0011	0.8968	0.0041	0.8823	0.0048	0.8636	0.0068
15	0.9503	0.0016	0.9328	0.0027	0.8698	0.0091	0.8568	0.0102	0.8118	0.0145
16	0.9420	0.0043	0.9206	0.0067	0.8473	0.0218	0.8436	0.0240	0.8189	0.0456
17	0.9341	0.0127	0.9085	0.0198	0.8249	0.0623	0.8227	0.0660	0.9165	0.2277
18	0.9249	0.0517	0.8953	0.0737	0.8022	0.2116	0.8080	0.2147	1.1456	1.4042
19	0.9185	0.1577	0.8859	0.2268	0.7864	0.6417	0.7985	0.6718	1.5560	6.6217
20	0.9041	0.8190	0.8696	0.9997	0.7627	2.4507	0.7794	2.5014	2.1198	27.1412

Variance of Relatives and 'F' from Comparison to Population Variance

Threshold	Males and Females		Males only		Females only	
	s^2	F	s^2	F	s^2	F
2	638150	2.1134	745756	2.3645	709406	2.5382
3	602769	1.9962	638975	2.0259	625712	2.2388
4	565069	1.8713	608112	1.9280	583894	2.0892
5	536081	1.7753	570106	1.8075	553275	1.9796
6	493712	1.6350	514681	1.6318	497206	1.7790
7	444325	1.4715	470256	1.4910	433319	1.5504
8	385200	1.2757	406450	1.2887	364150	1.3029
9	326762	1.0821	355231	1.1263	298512	1.0680
10	289331	1.0436	312275	1.0099	260362	1.0731
11	271019	1.1141	288900	1.0917	244812	1.1413
12	265006	1.1394	277737	1.1355	239725	1.1655
13	265150	1.1387	273844	1.1517	242506	1.1522
14	270712	1.1153	276581	1.1403	248256	1.1255
15	282400	1.0692	278681	1.1317	268750	1.0396
16	302800	1.0028	300144	1.0508	288419	1.0319
17	334394	1.1074	325994	1.0336	307819	1.1013
18	394850	1.3076	394281	1.2501	315395	1.1285
19	443456	1.4686	442419	1.4027	466150	1.6679
20	566487	1.8760	529525	1.6789	737662	2.6393

General population variance:

- males and females = 301,950
  sample size = 412,100
- males = 315,395
  sample size = 210,950
- females = 279,418
  sample size = 201,150