II. THE SAMPLE

The preceding section dealt with estimation of the frequency and types of twins in a population at various ages. Such estimates are important for large twin studies if twin samples are to be compared with the respective parent populations in any respect. For this purpose, population statistics should be based upon numbers of twin individuals rather than of twin pairs, because after the first year of life the relative frequencies of twin individuals are not altered by mortality or migration. Within twin samples themselves, additional statistical problems arise, but some of these, too, may be circumvented by expressing all frequencies in terms of twin individuals. In this connection, several consequences of the sampling process in twins may be explored with profit.

Frequency of Twins and Zygosity Types in Samples

When twins are to be studied in a sample of a population including nontwins, it is important to know if the sample contains a representative proportion of twins, and if the twins themselves are representative of all twins in the population. Even when a sample consists entirely of twins, it is often possible, for the purpose of this comparison, to estimate the number of nontwins encountered during collection of the sample. On the other hand, if the sample is composed entirely of persons affected by a medical condition, the twins may not be representative of all twins, but it is enough to show that they are representative of affected twins.

For convenience in this discussion, the population twin rate is taken as two per cent, and the proportion of twins from opposite-sex pairs is assumed to be one-third of all twins. A sample which differed significantly from the parent population in either of these two characteristics would be regarded as selected and unrepresentative. However, it is important that the statistics be based upon twin individuals, because even random and representative samples may deviate significantly from the parent population in corresponding statistics based upon pairs. A consideration of different kinds of samples will illustrate the inadequacies of the second type of statistics.

Some samples will resemble the parent population with either kind of analysis. This would be true, for instance, if one were to compare the frequency of twins in the general population with the frequency of twins among children born to mothers under age 20. If one obtained records for a given city on all children between one and five who had been born to such mothers, twin partners would usually enter the sample together. In this respect they would present the same proportion of complete pairs as in the remaining population. It would therefore be correct to compare the frequency of twin pairs in the sample, whether represented by one or by two twins, with the same statistic for twin pairs between ages one and five born to all mothers, which would be approximately one per 100. A significantly different frequency of pairs in the sample would call for biological interpretation.

By contrast, most samples are likely to differ from the parent population at least with respect to the frequency of twin pairs as compared to nontwins. For instance, if an ideally random sample is such a small fraction of the parent population that individual probabilities of inclusion are low, nearly every twin index case will represent a different pair. The proportion of twins in the sample will still be two per cent, so that the number of twin pairs represented will be two per 100, instead of one per 100 as in the parent population.

In both types of sample the ratio of same-sex to opposite-sex pairs would normally be 2:1, whether the calculation was based on index cases or on pairs represented. For either method of calculation, a significant deviation from this ratio would indicate some error in sampling. However, when a sample is selected on the basis of a condition in which MZ and DZ twins have different concordance rates, only the calculation based on index cases is expected to give a 2:1 ratio. Among mongoloid defectives, for instance, all MZ twins may be concordant, and nearly all DZ twins, discordant. If mongolism is not more frequent in twins than in the general population, the proportion of twins in the entire sample should be about two per cent. One-third would belong to opposite-sex pairs and twice as many, or two-thirds, would belong to DZ pairs. If, however, ascertainment[2] of mongoloids in the given population is nearly complete, the MZ twins, being concordant, would represent half their number of pairs, while the DZ twins would represent one pair each. If this sample of mongoloids contained thirty individuals, they would comprise, in the average sample, five complete pairs of MZ twins and twenty half-pairs of DZ twins (except for the rare concordant DZ pairs). This ratio, 1:4, would be quite different from the expected 1:2. If half the DZ pairs were of opposite sex, the sample would contain 10 opposite-sex pairs and 15 same-sex pairs, in a ratio of 2:3. Larger samples would confirm these unexpected ratios. Hence, even in a sample obtained by complete ascertainment of mongoloids in a population, the frequency of twin pairs would exceed expectation (in the above instance there are 25 instead of an expected 15 pairs), and the proportion of monozygotic pairs would be much smaller than in the general population.

Whether ascertainment is complete or incomplete, the probabilities of inclusion in the usual types of twin sample are not entirely independent for twin partners. Twins, and especially MZ twins, tend to have similar living habits and are more likely than unrelated individuals to be concordant with respect to conditions under study. The factors bringing one twin into a sample are likely to bring in his partner, too, especially if the twins are monozygotic. It follows that the number of pairs represented by two cases each will be greater than anticipated on the basis of chance. It does not follow that the number of twin individuals will exceed expectation, because, if similarity of living habits can bring some pairs into the study together, it will just as readily keep pairs out of the study together.

[2] Ascertainment, as used here (cf. Shull, 1954) means detection of individuals who meet the given criteria; usually, «affected» individuals. However, detection of secondary cases in a family by means of the primary case is not included under the term. Complete ascertainment implies detection of all affected individuals in the population, each independently. Double ascertainment of a twin pair occurs when each partner is independently reported.

In addition to the above factor, other influences determining the proportion of doubly-ascertained pairs in a sample are the concordance rates for the conditions studied and the completeness of ascertainment of affected persons in the population. Since these variables are difficult to evaluate, it is usually not possible to compute an expected ratio of twin individuals to twin pairs, or an expected number of pairs in the sample.

Irrespective of deviations from the population in the frequency and types of twin pairs, the frequency and types of twin index cases are expected to be constant for all representative samples. A representative sample, for this purpose, is one in which the ascertainment rate is the same for twins and nontwins (if nontwins are recorded in the study), the same for twins with affected partners and for twins with unaffected partners, and the same for MZ and DZ twins. Unless the condition under study can be shown to have different frequencies in twins and in nontwins, or different frequencies in MZ twins and in DZ twins, deviations from standard frequencies for the given population are presumptive evidence of preferential ascertainment of certain categories. In particular, if the proportion of index cases coming from same-sex pairs is significantly more than two-thirds, ascertainment may have favored same-sex or MZ pairs. Or it may have favored pairs concordant for the condition, because if concordant pairs are more often monozygotic, such selection would increase the number of same-sex pairs. For the last reason, a sample containing an excess of same-sex cases does not furnish reliable estimates of concordance rates unless the bias can all be attributed to selection of same-sex or MZ pairs as such. It may be noted, however, that an excess of cases from same-sex pairs may be traceable to the counting of some affected cotwins as index cases when they are in fact secondary cases. If this error is corrected, the data may then supply valid concordance rates.

Because of the difficulties encountered in the detection of persons who lost a twin partner at birth or in infancy, some twin samples include only intact pairs. Under these circumstances it cannot be judged whether the sample is representative because, as was explained in the preceding section, accurate comparative data are not obtainable on the frequencies of intact twin pairs in a population after infancy. It is therefore always desirable to sample intact pairs and broken pairs alike, at least in the initial registering of the cases. The degree to which this is achieved may be assessed by comparing the observed proportion of stillborn cotwins with that in an appropriate twin population. If broken pairs are underrepresented, concordance with respect to survival may have influenced ascertainment, and should be allowed for.

Weinberg's differential method is sometimes used to estimate the proportion of MZ twins in a sample, for comparison with the expected proportion. This procedure is generally unnecessary and even undesirable for the reason that the differential method doubles any sampling error in the observed proportion of opposite-sex pairs. As a consequence, the deviation in the estimated proportion of MZ twins may appear statistically significant unless due allowance is made. The observed proportion of opposite-sex cases offers the same amount of statistical information as the estimated proportion of MZ cases, and the former can be compared directly with the primary datum for the parent population.

Class Frequencies within a Twin Sample

It can be stated as a general rule that twin data should be expressed in terms of index cases. This principle is illustrated again in the case of a twin sample which is to be compared with single-born persons in terms of relative or absolute frequencies of different classes within the sample; for instance, with respect to medical diagnoses. In a large and representative sample, the number of twin index cases in each category will be proportional to the frequency of the respective category in all twins. Class frequencies can therefore be studied from index cases.

In some instances, as when quantitative intra-pair differences are concerned, it may be preferable to work with the number of pairs represented rather than with index cases. If this is done, however, statistical problems are multiplied. The problem most relevant to this discussion is that of comparing twins to nontwins with respect to proportions in different sub-groups.

Within a series of twins, each diagnostic sub-group may be regarded as an independent twin sample, within which the ratio of pairs to cases will depend upon the values of the three variables specified in the preceding section: concordance rate with respect to the trait used in ascertainment, interdependence of ascertainment for concordant partners, and completeness of ascertainment. If all classes are ascertained in a uniform manner, the second and third factors may be held nearly constant, so that any distortion in the distribution of twin pairs can be ascribed to class differences in concordance rates. Classes with high twin concordance rates will include many pairs represented by two index cases, and the ratio of pairs to cases will approach 1:2, while in classes with low concordance rates the ratio may be 1:1. Thus, although the index cases might accurately represent the class frequencies in the general population, the pairs formed by them might show a very different distribution.

In order to illustrate this point, recently reported figures on mentally defective twins (Allen and Kallmann, 1955) are given in table 2. Data on distribution of twin pairs have

Table 2 - Distribution of Institutional Diagnoses in Mental Defectives; Comparison of Twins with Nontwins

Diagnostic Classification	Nontwins		Twin Patients			The Same Twins Taken as Pairs		
	Number	Percent	Number	Percent	χ^2	Number	Percent	χ^2
Undifferentiated	16400	72.5	276	70.1	0.3	195.5	65.2	2.2
Mongolism	1406	6.2	22	5.6	0.3	19	6.3	0.0
Cranial Anomaly	686	3.0	18	4.6	3.1	16	5.3	5.2
Cerebral Palsy	704	3.1	23	5.8	9.4	19.5	6.5	11.1
Post-infectional	910	4.0	4	1.0	8.9	4	1.3	5.4
Post-traumatic	997	4.4	32	8.1	12.3	32	10.7	26.7
Miscellaneous	1527	6.7	19	4.8	2.2	14	4.7	1.9
Total	22630	99.9	394	100.0	36.5	300	99.7	52.5

been added for comparison with the distribution of index cases. In view of the fact that some of the twins diagnosed by the schools as *familial defectives* would have been considered *undifferentiated* but for their concordant twin partners, the two diagnostic groups have been combined in order to assure comparability of twins and nontwins. Although it may not be quite correct to use chi-square for comparing twin pairs with single-born individuals, the resulting error is negligible in this instance. The value of chi-square for twin cases, 36.5 with six degrees of freedom, is highly significant, showing that the distribution of diagnoses is different for twins and for nontwins even in the most favorable comparison. However, the distribution of twin *pairs* is distorted by differences in concordance rate from one diagnostic group to another, and this distortion expresses itself, in the last column, as a marked increase in chi-square, despite the reduced number of observations.

Twin Concordance Rates

If ascertainment of affected twins is complete for the population, a direct count will give the proportion of pairs with two affected partners. This is the concordance rate as the term is usually understood (Luxenburger, 1940 a). The number of concordant pairs is, of course, one-half the number of cases observed in these pairs.

In the case of incomplete ascertainment of affected twins, the sample should, ideally, be a miniature population with the same structure as the parent population. In the parent population of twins every concordant pair is represented twice. This is not true in the usual twin sample, where the process of ascertainment may select one twin from each of two concordant pairs instead of both members of one pair. Consequently, many concordant pairs are represented by a single index case and the number of pairs included is spuriously large. This distortion can be corrected if index cases from concordant pairs are, in effect, rearranged to form complete pairs. The resulting number of pairs may be used in estimating the concordance rate. In the calculations, the number of discordant pairs will equal the respective number of index cases, just as if ascertainment were complete. Also, as under complete ascertainment, the number of concordant pairs will be one-half the number of index cases belonging to such pairs. If the number of index cases from concordant pairs is designated as C and the number of those from discordant pairs as D, the calculation is expressed by the following formula:

$$\text{Twin concordance rate, } c = \frac{\frac{1}{2}C}{\frac{1}{2}C + D} = \frac{C}{C + 2D} \quad (1)$$

The method can be explained in another way. Among affected individuals in the general population, all concordant twin pairs are doubly represented, discordant pairs singly represented. Any adequate sample, maintaining the original proportions, will likewise have a twofold representation of the concordant pairs. The ratio of concordant to discordant pairs in the population will be just half as great as the ratio of concordant to discordant index cases in the sample (considering index cases as concordant or discordant according to the type of pair they belong to). A consistent estimate of the concordance rate in the population may therefore be obtained from a sample by halving the ratio of concordant to discordant index cases. Evidently, for the purpose of estimating twin

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concordance rates, index cases must be carefully classified to include affected cotwins only when they are independently ascertained.

The presence of two affected cases in each concordant twin pair may not exactly double its chances of representation in the sample (Shull, 1954). For conditions which do not attract much more attention to concordant twins than to single cases, the factor may be less than two. In instances where concordance itself renders affected pairs particularly burdensome to the family, or particularly interesting to physicians, concordant pairs are likely to be represented in excess. Such a bias in favor of concordant pairs would result in a deficiency of opposite-sex cases or, if zygosity has been determined, in an excess of monozygotic pairs. Precise formulae might be designed for these contingencies, but their usefulness would be limited.

The sampling variance of the concordance rate as estimated with formula (1) may be found by applying the general formula for sampling variance (Fisher, 1946) and the relations,

$$C = \frac{2cn}{1+c} \text{ and } D = n - C.$$

Here, n is the number of index cases or, more precisely, the number of cotwins observed as to concordance or discordance. The formula obtained for sampling variance is

$$V_{(c)} = \frac{c(1+c)\ (1-c^2)}{2n} \quad (2)$$

The result obtained by the proposed method of evaluating concordance differs from the results of two other methods that have been used, namely, simple tabulation of the concordant and discordant pairs observed, and the proband method (Weinberg, 1927). A simple tabulation of all pairs represented in the sample will approach the correct concordance rate if nearly all affected cases in the population enter the sample. This estimate can be represented as

$$c' = \frac{C-G}{C-G+D} = \frac{C-G}{n-G} \quad (3)$$

where C and D are again the numbers of individuals from concordant and discordant pairs, respectively, G is the number of doubly ascertained concordant pairs, and n is the number of index cases. If most of the concordant pairs are represented by a single case, G becomes small and the estimate approaches that obtained by Weinberg's proband method. In the latter, doubly ascertained pairs are counted twice:

$$c'' = \frac{C}{C+D} = \frac{C}{n} \quad (4)$$

The estimates[3] obtained by formulae (1), (3) and (4) are compared in table 3. The

[3] Formulae (1) and (4) may be compared directly with formulae (15) and (3a) in a previous paper (Allen, 1952), except that in the previous paper the symbols represented *pairs* of twins under the assumption of complete ascertainment. The first and last columns of table 2 in this paper correspond to the first and second columns of table 5 in the previous paper. However, the figures in the first line were incorrect in the first paper and should have been 10, 18 and 33 per cent instead of 10, 22 and 40 per cent.

values in the first column, representing parameters to be estimated, have been selected arbitrarily. The remaining columns have been obtained by means of the relation,

$$c' = \frac{c(2-a)}{1 + c(1-a)}, (5)$$

where a represents the proportion of the affected population ascertained. Formula (5) presupposes that double ascertainment of concordant pairs occurs only by chance, according to the square of the ascertainment rate. If, as is usually to be expected, double ascertainment occurs more often than merely by chance, a study in which the rate of ascertainment was a' would yield an estimate corresponding, in this table, to a value of a greater than a'. However, ascertainment rate does not affect the first estimate, c (formula 1).

Weinberg's proband method is useful in studies which require estimates of morbidity expectancy rather than of actual concordance rates. The distinction between these two estimates can best be illustrated in a more familiar situation, the distribution of a recessive trait in sibships of two. Here the morbidity expectancy is clearly 25 per cent for all children of two heterozygous parents. In *affected* sibships of two, however, the observed morbidity will be 57 per cent, much more than expected, and the concordance

Table 3 - Comparison of true concordance rates in twin populations and the respective concordance rates appearing among pairs represented in samples of different sizes. Formulas and symbols are explained in the text. [4]

Concordance Rate in the Twin Population, or as Estimated by $c = \frac{C}{C+2D}$	Concordance Rate among Sampled Twin Pairs $c' = \frac{C-G}{n-G} = \frac{c(2-a)}{1+c(1-a)}$: 90% ascertainment (a = .9)	50% ascertainment (a = .5)	10% ascertainment (a = .1)	Analysis by the Proband Method (or when a O) $c'' = \frac{C}{n}$
.05	.055	.073	.091	.095
.10	.109	.143	.174	.182
.25	.268	.333	.388	.400
.50	.524	.600	.655	.667
.75	.767	.818	.851	.857
.90	.908	.931	.945	.947
.95	.954	.966	.973	.974

[4] Luxenburger (1940b) published a table which has some values in common with our table. The resemblance is only superficial, however; the last four columns of our table are concordance rates that may be directly observed in a sample, equivalent to Luxenburger's x (or K′), while the corresponding columns in Luxenburger's table are estimates of penetrance, y (or M) derived from observed concordance rates. It is of interest that Luxenburger's formula is based on pairs represented instead of on index cases. As the present paper illustrates, this approach almost always leads to a complicated situation. As might be expected, therefore, the value of M can be obtained from observational data more simply by means of Weinberg's proband method (formula 4).

rate will be only 14 per cent. For, on the average, every sixteen pairs will include one with two affected: $(\frac{1}{4})^2 \times 16$; six with one affected: $2 \times \frac{1}{4} \times \frac{3}{4} \times 16$; and nine with none affected: $(\frac{3}{4})^2 \times 16$. Among every seven affected pairs, eight individuals are affected and only one pair is concordant. If it is assumed that the two types of affected sibships are sampled in proportion to the number affected in each, both the true morbidity expectancy and the true concordance rate can be estimated without knowledge of the ascertainment rate. Thus, the proband method by formula (4) would find two affected cotwins among eight; formula (1) would halve the number of concordant index cases and obtain a ratio of one to seven as the concordance rate.

In the case of dizygotic twins, Weinberg's proband method estimates the morbidity expectancy for people whose parents had the necessary genes, as in the above two-member sibships. When applied to monozygotic twins, the method is supposed to estimate the morbidity expectancy for people who themselves have the necessary genes; in other words, it is supposed to estimate the penetrance of those genes. However, the estimate obtained with this method is apt to be inaccurate, because it is based only on people who have an affected cotwin. Although this topic has been discussed by many authors, it deserves elaboration again in this connection. Hereditary traits with incomplete penetrance may be suppressed sometimes by environmental factors, sometimes by genetic factors, and sometimes by a combination of these. Since MZ twins have the same genotype, they are of no assistance in measuring suppression by genetic factors. Even suppression due to environmental factors is underestimated, since the environmental differences between twins are only a fraction of environmental differences between unrelated individuals. The index cases have in all cases experienced an environment favorable to expression of the trait, and the similar environment of the cotwin is also likely to favor penetrance. Consequently, any estimate of penetrance based on identical twins must be regarded as a probable overestimate, or as the upper limit of the range in which the true penetrance may lie. To some extent the same reservation applies to the estimate of morbidity expectancy obtained for DZ twins and, in fact, to any estimates of penetrance ormorbidity expectancy based on individuals closely related to affected cases, except as such relationship is specified.

In studies which call for a comparison of morbidity expectancies between twins of index cases and siblings of index cases (Kallmann, 1954) it is correct to apply the proband method to both sets of data. In general, differences between MZ and DZ twins will have the same statistical significance whether evaluated in terms of concordance rates or morbidity expectancy.

Several authors (von Verschuer, Schinz, Lasker) have proposed formulae for penetrance based on concordant pairs represented in a sample. Luxenburger (1940b) has shown that such formulae require complete ascertainment of the population. As an alternative, however, the calculation of penetrance by means of these formulae may employ an estimate of the true concordance rate as given by formula (1).

Unlike the upper limit of penetrance, which may only occasionally correspond to true penetrance, the twin concordance rate is a population parameter, subject to consistent estimation. In general, therefore, it would seem best to express twin morbidity data in terms of estimated concordance rates. Further conclusions, properly to be regarded as interpretations of the concordance rates, should be supported by additional data.

Summary, Part II

The statistics describing a twin sample should be computed from index cases (probands) rather than from twin pairs, if some or many pairs are represented by a single index case. Only then can the sample be compared with a larger population either in terms of twin frequency or in terms of proportions within the sample. The latter comparison might involve the proportions of opposite-sex and same-sex pairs, the proportions of monozygotic and dizygotic pairs, or the proportions of diagnostic subgroups. The same type of computation is also required for the estimation of penetrance and concordance rates. In the latter case, however, the number of index cases from concordant pairs should be halved in order to correct for the twofold representation of concordant pairs in the sample.

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SOMMARIO II

Le statistiche che descrivono un campione gemellare dovrebbero essere computate sui casi indice (probandi) piuttosto che sulle coppie gemellari, se alcune o molte coppie sono rappresentate da un singolo caso indice. Solo allora il campione può essere comparato con una più vasta popolazione sia in termini di frequenza gemellare che in termini di proporzione entro il campione. Quest'ultima comparazione può comprendere le proporzioni di coppie di sesso opposto e dello stesso sesso, le proporzioni di coppie monozigotiche e dizigotiche, o le proporzioni di sottogruppi diagnostici. Lo stesso tipo di computo è anche richiesto per la valutazione dei rapporti di penetranza e concordanza. In questo ultimo caso tuttavia, il numero dei casi indice dalle coppie concordanti dovrebbe essere dimezzato allo scopo di correggere la duplice rappresentazione di coppie concordanti nel campione.

RÉSUMÉ II

Les statistiques ayant pour but de décrire un échantillon gémellaire devraient être calculées en partant des cas index (probandi) plutôt que des couples gémellaires lorsque certains ou plusieurs couples sont représentés par un cas index particulier. Alors seulement l'échantillon peut être comparé avec une plus vaste population soit en termes de fréquence gémellaire, soit en termes de proportions entre l'échantillon. Cette dernière comparaison peut comprendre les proportions de couples de sexe opposé et du même sexe, les proportions de couples MZ et DZ, ou les proportions de sous-groupes diagnostiques. Le même genre de calcul est également requis pour l'évaluation des rapports de pénétrance et de concordance. Toutefois, dans ce dernier cas, le nombre des cas index des couples concordants devrait être réduit de moitié dans le but de corriger la double représentation de couples concordants dans l'échantillon.

ZUSAMMENFASSUNG II

Wenn ein Zwillingsmaterial eine Reihe von Paaren enthält, die nur durch einen einzelnen Probanden vertreten sind, dann sollte es statistisch stets von der Zahl der Zwillingsprobanden und nicht von jener der Zwillingspaare ausgehen. Nur dann kann das Material hinsichtlich der Zwillingshäufigkeit oder anderer Zahlenwerte mit einer Allgemeinbevölkerung verglichen werden. Dieser Grundsatz erstreckt sich nicht nur auf das Verhältnis von gleich- zu ungleichgeschlechtigen Paaren, sondern auch auf das Verhältnie von eineiigen zu zweieiigen Zwillingen und auf die Prozentsätze diagnostischer Untergruppen. Dieselbe Regel gilt für die Berechnung von Penetranz – und Konkordanz-ziffern. Im letzteren Falle ist es natürlich erforderlich, die Zahl der von konkordanten Paaren gewonnenen Zwillingsprobanden zu halbieren, um die unvermeidliche Ueberrepresentation konkordanter Paare zu korrigieren.