A biometric study on the inheritance of twinning in human beings is reported. This problem was investigated in terms of data obtained from the archives of the Genealogical Society of the Mormon Church in Salt Lake City. The results supported the hypothesis that dizygotic twinning is determined by recessive genes, expression of which is limited to the female.

GENEALOGICAL STUDY OF HUMAN TWINNING

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"THERE is probably no human biological peculiarity which has been more widely discussed over the past hundred years than the phenomenon of twinning" (McArthur, 1953a). One of the key points of interest is the inheritance of this trait. The most widely accepted current theory about this is Weinberg's conclusion, reached in the early 1900's, that the inheritance of the capacity to produce twins can only be shown on the female side and in the case of dizygotic twins; and that the tendency to produce twins is probably recessive. However, other views have been expressed. Dahlberg (1926) agreed that the inheritance of the disposition to bear dizygotic twins exists in mothers, the hereditary disposition of fathers probably being of no importance; but he felt that inheritance of monozygotic twinning also probably exists, and the disposition can be present in both the father and the mother. Greulich (1934) believed that the hereditary factor existed only for dizygotic twins, but found the hereditary constitution of the father as important as that of the mother.

Recent work on the induction of ovulation by human gonadotrophins and the high proportion of multiple births resulting from the use of FSH and LH (Gemzell, 1964) has suggested that DZ twinning may be visible indication of excessive maternal pituitary gonadotrophic activity (Milham, 1964). At this time, however, no attempts have been reported which more directly relate the inheritance of twinning to the anterior pituitary.

Most of the work on this problem has concentrated on pedigree studies to detect differences in the frequency of twinning in different lines (Bonnevie and Sverdrup, 1926), on the study of twinning among the relatives of parents of twins (Greulich, 1934), and on the phenomenon of repeat frequency of twinning (Weinberg, 1902, 1909; Greulich, 1934; Dahlberg, 1952; and Bulmer, 1958). Only a few studies, which will now be reviewed, have investigated twinning among the children of twins themselves, an approach which has obvious statistical advantages.

Galton (1876), in the course of his study to distinguish between the effects of nature and nurture, reflected on the hereditary tendency toward twin-bearing. He commented that the parents of twins, who are themselves one of a pair of twins, are relatively few and con-

cluded that he could not "institute a direct comparison between two groups of children, one of whom were the offspring of fathers or mothers who themselves were of twin birth, and the other were not, because my material was insufficient."

Weinberg (1902) recorded data for 110 female twins who had been married for at least 20 years. In all, they had 464 births among which were 10 twin births or 2.2 per cent. Dahlberg (1926) commented: "This is not a very large increase, but all the same indicates the heredity of twinning." Slater (1948) reported briefly from data on 503 children of twins that the evidence from the children of twins and the children of sibs of twins was opposite, but he drew no conclusions from his findings.

Waterhouse (1950), whose sample of parents who were themselves twins is the largest on record to date (487 twins), but is self-selected and possibly biased, found "a much increased rate of dizygous twin production among females who are members of dizygous pairs although the rate among children of male twins does not differ from that in the general population." The twining rates per 100 maternities were 9.02 and 1.52, respectively. Waterhouse concluded: "Almost unequivocally we may say that a tendency to dizygous twinning is inherited through the female line."

McArthur (1952b) recorded family histories of multiple births for women attending an antenatal clinic in England, and observed that women who were twins had 403 children and eight twin births. Husbands who were twins had 347 children and six twin births. In her discussion, McArthur has suggested that the factors involved in dizygotic twinning are probably maternal recessives and that about one-fourth of all women in the population have the twin diathesis. Weber (1945) and Johansson (1932), both working with cattle data, had also postulated that the factors for twinning are maternal recessives. Penrose (1959) conjectured that it is quite likely that in human beings fraternal twinning results from the mother being homozygous for a rather common gene. McArthur calculated from her data that the gene frequency q of the twinning gene or gene complex d is 0.53 or q^2 is 0.28, and from other studies she obtained the following values for q^2:

0.25 (Weinberg, 1902)
0.15 (Dahlberg, 1926)
0.30 (Greulich, 1934)
0.30 to 0.40 (Waterhouse, 1950).

Morton (1962) has also supported Weinberg by producing evidence of a different kind. He studied the genetics of interracial crosses in Hawaii, on the basis of data on 179,285 babies born in Hawaii during 1948-1958, and concluded "the frequency of monozygotic twinning is not affected by race, while the frequency of dizygotic twinning is independent of the father's race but is greatly influenced by the race of the mother."

Purpose of Study and Sources of Data

Thus, although there is some consistency in the opinions expressed about the inheritance of twinning, for the most part conclusions were drawn from inadequate data. Investigation based on data adequate with respect to quantity and quality is still needed. Specifically, the purpose of the present study is to investigate the hereditary mechanism of twinning, as expressed through twinning rates in families of persons who are themselves twins and in the families of sibs of twins. The major hypothesis to be tested is that dizygotic twinning is determined by one or more recessive genes, expressions of which are limited to the female. If this hypothesis is supported, it becomes necessary to estimate the frequency of the gene involved.

Table 1—Children Born to Twins and to Their Sibs and Twinning Rates per 1,000 Maternities, Classified by Type of Parent

Type of Parent	No. of Persons	No. of Offspring	No. of Sets of Twins	Twinning Rates per 1,000 Maternities
Twin from male-male pair	948	4,827	60	12.59
Male twin from male-female pair	586	2,937	23	7.89
Female twin from male-female pair	365	1,548	26	17.08
Twin from female-female pair	605	2,649	28	10.69
All twins	2,522	12,046	138	11.59
Male sib of male-male twins	946	5,270	55	10.55
Male sib of male-female twins	842	4,479	58	13.12
Male sib of female-female twins	532	2,833	37	13.23
Female sib of male-male twins	484	2,184	23	10.64
Female sibs of male-female twins	528	2,339	39	16.96
Female sib of female-female twins	415	1,860	19	10.32
All sibs†	3,783	19,130	236	12.49
Total twins and sibs	6,305	31,176*	374	12.14

* Includes 4 sets of triplets.
† Includes cases where the sex of one member of the twin pair was unknown.

Up to the present time, the problem of obtaining sufficient numbers for studying twinning among the children of twins, which Galton described in 1876, has remained. However, the family records of the Genealogical Society of the Church of Jesus Christ of Latter Day Saints in Salt Lake City, Utah, which have recently been made available to us for research purposes, provide a unique source for large bodies of genealogical data. The society has on file the records of some four million families. The basic units of genealogical information are family record sheets which include among other items the following: for the husband—name, date and place of birth, date and place of burial, father's and mother's name, date and place of marriage; for the wife—similar information; for each child—sex, birth order, name, date and place of birth, date of death, date and place of marriage, and name of marriage partner. Members of the church are encouraged to include stillborn children on the family record sheets. The records of the society are so designed that if an individual's name which appears on the family record sheet under "children" is marked with an asterisk, this signifies that the individual appears as a parent on some other family record sheets in the archives. Therefore, twins who have married and their sibs who have married are readily identifiable and can be followed up easily. The collection of data on twins and their sibs proceeded systematically by examination of records which are filed alphabetically, and selection of those families with at least one twin marked with an asterisk (index families). Next, the searcher identified the records in which childen of the index families, whether twins or sibs of twins, appeared as parents of the next generation. The offspring of these twins and their sibs were then recorded.

To date, records on 2,012 index families have been analyzed; these included 2,522 individual twins and 3,783 sibs

of twins with family record sheets on file. Analysis of twin births among the children of these twins and their sibs comprises the major subject of the present investigation (Table 1).

In addition to data on twinning among the children of twins and children of the sibs of twins, data were collected from the archives of the Genealogical Society of the Church of Jesus Christ of Latter Day Saints on 7,420 families which included at least one set of twins. In the present study, these data provide the repeat twinning rate, i.e., the twinning rate among subsequent births of women who have had at least one set of twins. This information is needed to supplement data on gene frequency obtained in the main part of the study; the relevant rate is included in Table 2.

Results and Discussion

From Table 1 we see that the over-all twinning rate among the children of twins is 11.6 per 1,000 maternities. The highest rate is found among the children of female twins of unlike sexed pairs, 17.1 with a standard error of 3.4.* In contrast, rates among the children of male unlike-sexed twins are low, 7.9 with a standard error of 1.6. The difference in these two rates is statistically significant, and the comparison provides a direct test of the importance of the female parent in determining the occurrence of twinning in the offspring.

Like-sexed twins consist of both monozygotic and dizygotic twins; thus, one should expect that twinning rates among their children would be somewhat elevated, but not as much as for female unlike-sexed twins. The rates for FF twins are, in fact, lower than those for MM twins, but the standard errors are large and the differences fully accounted for by chance fluctuations.

Further support for Weinberg's hypothesis comes from the twinning rate among children of sibs. The rate for female sibs of unlike-sexed twins is 17.0; for male sibs, 13.1. Comparisons among sibs of like-sexed twins show small differences, but this is not surprising in view of the fact that the groups are heterogeneous with regard to zygosity and the standard errors large.

When we combine the data for unlike-sexed and hence dizygous twins and their sibs, we find that the children of males include twins in 81 out of 7,335 maternities (11.0 per 1,000), and the children of females in 65 out of 3,822 maternities (17.0 per 1,000). The difference in rate is 6.0 and its standard error 2.45.

We conclude from these data that female twins from dizygous pairs and female sibs of such twins show an in-

Table 2—Twinning Rates per 1,000 Maternities Classified by Parent's Relationship to Index Twins

Parent	Total Twinning Rate	Dizygous Twinning Rate*	
Male twin of MF twin pair	7.89	6.86*	
Female twin of MF twin pair	17.08	14.45*	15.70*
Female sib of MF twin pair	16.96	16.52*	
"Repeat" rate (rate among later maternities of women who have had at least one pair of twins)	33.2	44.3†	

* Dizygous rate is estimated by doubling the rate of MF twins.

† Dizygous rate is estimated by computing the twinning rate among later maternities of women who have had at least one MF twin pair. This rate is likely to be a slight overestimate, since monozygous twins are counted when they occurred subsequent to the birth of MF twins.

* The approximate standard error is computed as $r/\sqrt{n}$ where r=rate under consideration and n=number of sets of twins on which it is based.

creased twinning rate among their children, but male dizygous twins and their male sibs do not show this increased rate (see White and Wyshak, 1964, for further details).

Since dizygotic twinning appears to be inherited, we now investigate the hereditary mechanism for twinning and estimate gene frequencies. Although the theory of maternal recessiveness is the most widely accepted one at present, it is desirable to investigate the consequences of other genetic hypotheses. Therefore, the following single-gene hypotheses will be explored from the data of this study:

(1) maternal autosomal recessiveness
(2) maternal autosomal dominance.

Using Li and Sacks's (1954) methods, we have drawn up the table below to show the probability, under the two hypotheses listed above, that a female denoted by X has a specified genotype. The probability is conditional on the given information about X or her relatives.

We have the following data: twinning rates in families of women who are themselves dizygous twins; twinning rates in families of men who are dizygous twins; and "repeat" twinning rates for mothers who have had dizygous twins.* "Repeat" twinning rates are here defined as the proportion of twins among later maternities of women who have had at least one set of twins.

The following assumptions are made:

(a) Dizygous twinning can occur only when the mother has genotype dd under the hypothesis of maternal recessiveness; only when the mother has genotype DD or Dd under the hypothesis of maternal dominance.

(b) Male dizygous twins mate randomly with women in the general population. Thus, the probability of twin children among their offspring is determined by their wives, viz., q^2 under the hypothesis of recessiveness, $1-q^2$ under the hypothesis of dominance.

If we ignore the effect of maternal age and other factors affecting the expression of genes, the probabilities of specified genotypes should be proportional to the twinning rates observed, since the occurrence of a twin birth is an indication that a woman has the proper genotype for twinning. Thus, comparisons of twinning rates in various groups will indicate the relative proportions of the twinning genotype for the groups. On the basis of such comparisons, estimates of gene frequencies will be made.

With the data at hand the consistency of the two hypotheses will be explored.

A. Under the hypothesis of maternal recessiveness, the twinning rates should be in the following proportions: $q : q^2 : 1$ for female DZ twins, male DZ twins, and "repeat twinning" rates, respectively.

(a) Consider first the corresponding total twinning rates which are from Table 2, 17.1, 7.9, 33.2. These are in the ratio

* If data on other classes of relatives were available, it would be possible to investigate the consequences of the genetic hypotheses of maternal sex-linked recessiveness and maternal sex-linked dominance.

Given Information on X or Her Relatives	Hypothesis 1 P(X Has Genotype dd)	Hypothesis 2 P(X Has Genotype DD or Dd)
X is a DZ twin	q	$\frac{1+pq}{1+q}$
X is a sib of DZ twins	q	$\frac{1+pq}{1+q}$
X is mother of DZ twins	1	1

0.515:0.238:1. Three separate estimates may be made of q:

(1) Solving the equation $q/1=0.515/1$, which is obtained by relating the rate of female DZ twins with the repeat rate we find a value for q:
$q=0.515$

Also, $0.515^2=0.265$ which is close to 0.238, the figure obtained for q^2.

(2) Solving the equation $q/q^2=17.1/7.9$ which relates rate for female and male DZ twins
$q=0.462$

(3) Solving $q^2/1=0.238/1$ which relates rates for male DZ twins and the repeat rate
$q=0.488$.

(b) We turn next to estimates based on dizygous rather than total twinning rates. The dizygous rates are 14.5, 6.9, and 44.3, which are in the ratio 0.327: 0.156:1. When these values are inserted in the equations above, the estimates of q are:

(1) $q=0.327$
(2) $q=0.476$
(3) $q=0.395$.

B. Under the hypothesis of maternal dominance, the rates should be in the proportions:

$(1+pq)/(1+q):1-q^2:1$.

Solving for q in a manner analagous to that above, we have, using the total twinning rates:*

(1) $q=0.980$
(2) $q=0.847$
(3) $q=0.874$.

Using the dizygous twinning rates, we find the following values for q:†

(1) No solution, q is greater than 1 or negative
(2) $q=0.841$
(3) $q=0.919$.

One also observes from Table 2 that the total twinning rates for female DZ twins and their sisters are 17.1 and 17.0 per 1,000 maternities, a finding consistent with both genetic hypotheses, recessiveness and dominance, since according to each hypothesis the gene frequencies should be the same. The dizygous rates for these two classes of women are also about the same—14.5 and 16.5. The rates for the sisters may be used instead of the rates for the twins themselves to provide additional independent estimates of q.

Table 3 summarizes the estimates of

* For (1) the second root is $q=-0.495$; for (2) the second and third roots are imaginary; for (3) the second root is $q=-0.874$.

† For (2) the second and third roots are imaginary; for (3) the second root is $q=-0.919$.

Table 3—Estimates of q Under Hypotheses of Maternal Recessiveness and Maternal Dominance

Comparisons Made	Maternal Recessiveness q based on:		Maternal Dominance q based on:	
	Total Twinning Rates	Estimated DZ Twinning Rates	Total Twinning Rates	Estimated DZ Twinning Rates
Female DZ twins: repeaters*	0.515	0.327	0.980	No solution
Sisters of DZ twins: repeaters*	0.512	0.372	0.985	No solution
Female DZ twins and sisters pooled: repeaters*	0.514	0.354	0.982	No solution
Female DZ twins: male DZ twins	0.462	0.476	0.847	0.841
Male DZ twins: repeaters*	0.488	0.395	0.874	0.919

* Repeaters are women who at some time have produced twins and have had subsequent children including twins.

q under the two hypotheses for the comparisons discussed above. In brief, under the hypothesis of maternal recessiveness the estimates of the gene frequency, q, for the twinning gene, d, fall within a fairly narrow range—between 0.33 and 0.52—and are consistent with the speculations and findings of other investigators. In contrast, the results under the hypothesis of dominance, particularly the fact that there is no solution for q, lead to the rejection of this hypothesis. The analysis discussed above explores twinning by postulating a single-gene mechanism. It may well be that multiple genes are involved; certainly maternal age and possibly other factors operate in the production of twins; nevertheless, the lack of bias due to self-selection and the size of the sample analyzed provide firm support for the provisional theory that twinning results from the mother being homozygous for a gene which is rather common, occurring in one-fourth of the female population.

We are currently in the process of obtaining information on twinning in a third generation, that is, among the grandchildren of dizygous (unlike-sexed) twins and their sibs. Such data will enable us to investigate more conclusively the hypotheses on the inheritance of twinning which have so far been borne out by our study of twinning among the children of twins and their sibs, and to consider the role of gonadotrophins in the production of dizygous twins.

Summary

The inheritance of human twinning was studied by investigating (a) twinning among the children of twins and their sibs; and (b) the repeat twinning rates. The data were obtained from the archives of the Genealogical Society of the Church of Jesus Christ of Latter Day Saints at Salt Lake City, Utah. The major hypothesis tested was that dizygotic twinning is determined by one or more recessive genes, expression of which is limited to the female.

The results of this study supported the hypothesis. The twinning rates among children of female dizygous twins and their female sibs were significantly higher than those for male dizygous twins and their male sibs. Under the single gene hypothesis of maternal recessiveness, an estimate was made of q, the frequency of the twinning gene. The value obtained for q was in the range from 0.33 to 0.52, the estimate of q^2 therefore being from 0.11 to 0.27. The results led to rejection of the single gene hyopthesis of maternal dominance. The level of rates indicates that if twinning is controlled by a single gene, the rate of penetrance is low.

In the future we expect to investigate more fully the hypotheses developed by considering twinning among the grandchildren of dizygous twins and their sibs and to consider the role of gonadotrophins in the production of twinning.

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