Consanguineous Marriages in the Chicago Region[1]

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AMONG THE PROBLEMS in the study of human genetics is the appraisal of the "load of mutations" that is carried by an average man. The children of a consanguineous marriage will have a greater than average chance of receiving the same rare recessive gene from both of their parents. This situation occurs because the common ancestors of the parents might have carried and transmitted to both parents various rare genes. In this paper we will estimate from the increase of deaths and abnormalities in consanguineous families the average number of rare recessive genes present in a human being.

The study of consanguinity has a long history, with its scientific aspects going back a century to the work of Bemiss (1858). Bemiss clearly saw that his data were influenced by selection, that is, that he would be told of the children of consanguineous persons more frequently if they were abnormal than if they were normal. Since that time, various authors have attempted to avoid this type of bias. Mitchell (1865) employed both of the methods that have since proven successful for others: (1) he made a study of all marriages in a given population, locating the consanguineous ones in that manner, and (2) he studied the ancestry of all persons with a certain ailment (lunacy) in a large area.

In the Roman Catholic Church, close consanguinity is an impediment to marriage. A dispensation is required before an ecclesiastically valid marriage is possible. Utilizing this fact, Orel (1935) introduced a refinement of Mitchell's first method by locating consanguineous marriages through the records of dispensations in the Roman Catholic Archdiocese of Vienna. Similar investigations have been carried out in France by Sutter and Tabah (1952) using the records of the Dioceses of Blois and of Vannes.

SOURCES OF THE DATA

This study has been made with the help of the records of the Roman Catholic Archdiocese of Chicago. Records of dispensations from the impediment of consanguinity to marriage (*impedimentum consanguinitas in gradu secundo*), have been obtained for the twenty years between 1936 and early 1956. Information on 239 marriages was gathered in this manner. Of these, 78, or one-third of the families, were not available to us because either, as in five cases, they refused an interview, or they are known to have moved to another part of the country, or else their present whereabouts are unknown.

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Not all of the remainder of the marriages have proven useful for this study. Because of the small numbers concerned and the loss of information with increasing distance of relationship, the 17 families in which the relationship was more distant than that of first cousins have been omitted. In 12 additional families the relationship was one of affinity (relationship through marriage), rather than consanguinity.

In 23 marriages there was little likelihood of children from the outset because of the advanced age of one or both of the participants. These have been omitted, as was one case in which the exceedingly poor health of the wife probably precluded consummation of the marriage. Seven additional cases were referred to an interviewer by their pastors at the time that the pastors were being consulted about cases in the Archdiocesan files. Because their irregular ascertainment probably does not bias the pertinent information about them, these cases have been included in this study.

In many cases, the marriage ceremony had been a religious validation of a previously contracted civil marriage. We decided to limit this work to the consideration of marriages contracted since 1920, as many of the data analyzable in this investigation (e.g., medical care of children) were very different after World War I from what they had been in the years previous to it. Fortunately, only six families had to be discarded because their civil marriage took place prior to 1920.

All subsequent statements are based on the remaining 109 consanguineous families. Of these, 106 are marriages between first cousins, one is a marriage between double first cousins, and there is one uncle-niece and one aunt-nephew marriage. Among the 107 consanguineous families for which adequate data exist, 25 had a civil marriage at least one year prior to the religious validation of the marriage and in five additional cases they lived together as man and wife for some time without formal marriage.

During the interview of each consanguineous family, a brief description was made of the sibships of the husband and wife. A control interview was then arranged with one of the married sibs. To decrease selection in choosing the control, preference was given to an interview with a sister of the wife, and 50 controls of this type were obtained. Sometimes the wife did not have a married sister in the Chicago area, hence there were 32 additional controls where a sib of the husband or brother of the wife was used. In one instance, the control is a nephew of the wife. This gives a total of 83 control families. Most of the 26 other families did not contain sibs who could be used as controls. In a few cases, the consanguineous couples requested us not to derive a control from their immediate relatives.

The children of consanguineous marriages will be referred to as consanguineous children. The children of control marriages will be referred to as control children. The control and consanguineous children are related to each other both as first and as second cousins (e.g., if the consanguineous and control wives are sisters, then their children are first cousins. In this event, the husband in the consanguineous family is a first cousin of the wife in the control family and through this relationship the children are second cousins.). Because of the close relationship, the two groups of children are likely to represent a similar socio-economic status, which, it is hoped, would be reflected in similar medical care.

The interviews were carried out in the homes of the families concerned. The interviewers (R.H.R. and R.E.H.) are Catholic priests. They introduced themselves as priests and pointed out the statistical nature of the study and the fact that only they would know the source of the information. Almost without exception, they received full cooperation from the families.

For one consanguineous family the interview was conducted by mail. Information on another family was obtained from the parents and a sister of the husband. The information on one control family was supplied by the consanguineously married woman, who described her sister's family. These three families live in other parts of the country. Thus, for only one consanguineous and only one control family was there a failure to get information directly from one of the parents.

In general, the control couples were interviewed about a year after the consanguineous couples.

For some of the data, a special control population has been derived from that portion of the records of Cook County, Illinois, which concerns the city of Chicago. Selection was made of couples married during 1936 whose last name begins with the letter *A* and for whom there was an indication that the marriage had been performed by a Catholic priest. The distribution of consanguineously married couples by national origin probably is not random within the Catholic population of Chicago, as will be noted later. Family names beginning with the letter *A* have similar biases with respect to national origin. Birth records were searched for the succeeding nine years and the 133 families for which a subsequent first birth has been recorded have been used for certain items of information. This control group will be referred to as the county-records control.

RESULTS

Statistics of consanguineous marriages

The relatively low frequency of consanguineous marriages currently taking place in the United States may be seen from studies of Woolf *et al* (1956), who found somewhat less than one first-cousin marriage per thousand among Mormons and their non-Mormon relatives in the period since 1940. Their data indicate that over the past two centuries the frequency has declined with some regularity from a value about ten times the present rate. About half of the decrease has taken place in the last half century. Statistics do not appear to be available on the frequency of first-cousin marriage among American Roman Catholics relative to the population as a whole.

In figure 1 are given the numbers of marriages between first cousins observed each year since 1936. The year when first married is given as the year of marriage (if civil marriage preceded religious marriage), or, in the four pertinent cases, the year in which cohabitation without any marriage ceremony began. This method has been employed on the assumption that almost all of these marriages would have been under religious auspices from the beginning if it were not for the fact of consanguinity. Data on the number of marriages commencing prior to 1936 are incomplete and therefore have not been presented. Also shown in figure 1 for certain years are the

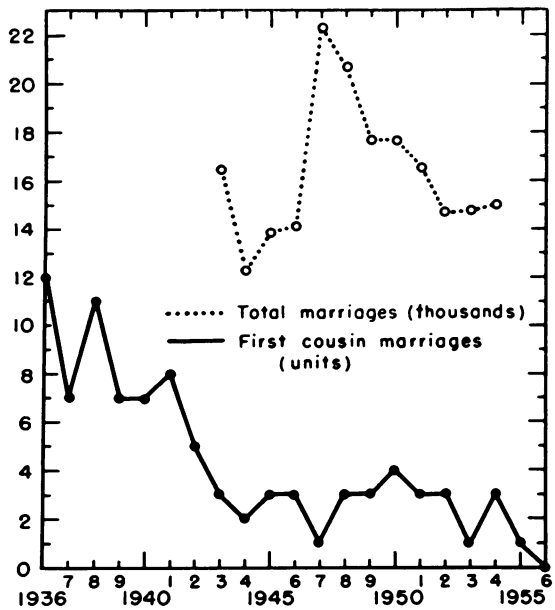

FIG. 1. The observed number of first-cousin marriages of the type discussed in this paper and the thousands of all marriages performed under the auspices of the Archdiocese of Chicago, Illinois, 1936–1956.

thousands of marriage ceremonies performed (dotted line) under the auspices of the Archdiocese of Chicago, as listed in The Official Catholic Directory (1943–1954). The first-cousin marriages are underrepresented because of the factors which militate against a religious ceremony for them and also as a result of the fact that not all first-cousin marriages have been included here (marriages involving elderly persons, and untraced and uninterviewed couples have been omitted). Figure 1 is so drawn that agreement of the two lines would indicate a frequency of one-tenth of one per cent for first-cousin marriages. Allowing for some additional cases to correct for underrepresentation, it appears that first-cousin marriages of the type discussed in this paper were at a level of less than one-tenth of one per cent at the beginning of this period and that they now are less frequent than one-twentieth of one per cent of all marriages in this Archdiocese.

National origins

Table 1 lists the major nationality groups represented among these consanguineous marriages, the nature of the consanguinity, and the number of liveborn children in each marriage. The marriages have been listed in the nationality category that provided the common ancestry. The "Other" group includes families of which there are three French or French-Canadian, two Mexican, one Puerto Rican, one Lebanese, one Norwegian, one Negro, one "old American" and two of unascertained national origin. Also shown in table 1 is the relationship between the consanguineous marriage

TABLE 1. NATIONALITY DATA AND NUMBER OF LIVEBORN CHILDREN AMONG THE CONSANGUINEOUS AND CONTROL FAMILIES

National origin	Type of consanguineous marriage*						Liveborn children							Control relationship*						Control Spouse of other National Origin	Liveborn Children							
	Total	1	2	3	4	other	0	1	2	3	4	5	6	Total	1	2	3	4	Other		0	1	2	3	4	5	6	8
Italian	45	7	16	8	12	U-N, A-N	9	11	17	6	2	—	—	35	5	21	3	5	1	8	4	8	17	5	1	—	—	—
Polish	18	5	5	4	4		5	5	4	2	—	2	—	15	1	10	2	2	—	4	1	5	3	4	2	—	—	—
Other East European	8	2	2	1	—	1 double first 2 unknown	—	3	3	1	1	—	—	3	2	1	—	—	—	—	2	—	1	—	—	—	—	—
German	13	3	5	5	—		2	1	6	2	—	2	—	11	—	9	—	2	—	9	1	2	2	1	1	1	2	1
Irish	13	3	5	3	2		3	1	4	2	—	3	—	9	2	4	1	2	—	7	2	1	5	—	1	—	—	—
Other	12	3	6	1	2		1	2	2	3	2	1	1	10	1	5	1	3	—	7	2	—	5	2	1	—	—	—
Totals	109	23	39	22	20	5	20	23	36	16	5	8	1	83	11	50	7	14	1	35	12	16	33	12	6	1	2	1

* See text for explanation of code.

and its control, the number of marriages in which the control propositus married a person of another national origin, and the number of liveborn children in each marriage. The type of consanguineous marriage is coded as:

(1) the husband's father and wife's father are brothers
(2) their mothers are sisters
(3) the husband's father and wife's mother are sibs
(4) the husband's mother and wife's father are sibs

The controls are related to the consanguineous families as the families of:

(1) the consanguineous husband's brother
(2) the consanguineous wife's sister
(3) the consanguineous husband's sister
(4) the consanguineous wife's brother

For the aunt-nephew marriage, the only satisfactory control was one of her other nephews, which accounts for the remaining control family.

It is possible that the high frequency of persons of Italian ancestry (who appear to form a much smaller proportion of the Catholic population of Chicago) is a reflection of the high frequency of consanguinity in Italy (Adamo, 1952).

It will be observed in table 1 that type 2 consanguineous marriages are about twice as frequent as those of any other type, the variation from a uniform frequency being significant ($\chi^2 = 8.85$, 3 d.f., $P < .05$). The observed frequencies of the four types of marriage are roughly the same for Italians and non-Italians ($\chi^2 = 4.23$, 3 d.f., $P > .05$, for Italian vs. non-Italian couples for the four types of first-cousin marriage). The other nationality groups do not show striking departures from the general pattern. The frequencies of the various types of marriage may be compared with those cited by Morton (1955). The excess of type 2 marriages is similar to that shown for the Japanese and Austrian data, but an excess of type 4 marriages has not been observed by us.

Most of the consanguineously married persons were born in the United States. In eight marriages both parties were born in another country, in 21 cases only the husband was born abroad, and in 13 cases only the wife was born abroad. Among the controls, eight couples were both born abroad, in 11 cases only the husband was born abroad, and in two cases only the wife was born abroad. The correlation between sibs in the control and the consanguineous groups and the selection for residence of controls in the Chicago area vitiate any statistical analysis on the proportion of foreign-born individuals in the two groups. Furthermore, an analysis with respect to the proportion of foreign born of marriageable age in the United States would be inadequate with the data that are available.

Marital status

In the consanguineous families, men of 29.4 ± 6.1 years of age (mean ± standard deviation) married women of 24.6 ± 5.2 years of age (based on 108 families). Among the control families marriage is earlier, men of 26.8 ± 4.8 years having married women of 22.8 ± 4.0 years (based on 82 families). The value of t for the difference between the mean age at marriage for each sex is highly significant ($P < .01$), being 3.29 for the men and 2.68 for the women. The analysis has not been made with any correc-

tion for the skewing due to the occurrence of a long tail toward the older individuals. The median age at marriage is slightly less in all groups, but the difference in age at marriage remains at 1.8 years for the women, though the mean difference, 2.6 years, decreases to a difference of 2.3 years in the median for the men.

The correlation between the ages of husband and wife at time of marriage is .67 for the consanguineous couples and .57 for the controls. The difference between these values is not significant. In about ten per cent of both groups the husband is younger than the wife.

Among the consanguineous families, four persons had previously been married. One man had a childless civil marriage, one man had been widowed with one child, one woman had been widowed with one child, and one woman had a previous marriage with one child. In an additional case, one of the women is raising an illegitimate child born before her marriage. Among the controls, the first marriage of the propositus has been used. The spouses of these propositi include one woman and two men who have previously been married but who did not have any children, one woman with a child by a previous marriage, and one woman with an illegitimate child born prior to marriage.

Among the 109 consanguineous families, seven marriages have been terminated by separation or divorce and seven by the death of one of the spouses. Among the 83 controls, six have been terminated by separation or divorce and seven by death. For all four of these groups of terminated marriages, about half of the families concerned were still within the age period during which one or more additional children might have been anticipated.

Not all of these investigated families have completed their child-bearing period. Forty of the consanguineous women and 27 of the control women have had a pregnancy terminate within the six years preceding the interview, which is an indication that a moderate proportion of the families will probably have one or more additional children. To the extent that abnormal children are positively correlated with parental age or birth rank, this failure to have complete families will introduce a bias into these observations so that the observed proportion of abnormal children may be a bit below the true proportion for these families.

Pregnancy

During the interview, each woman was asked about her children, and, at a later stage of the interview, about any dead children or lost pregnancies. The informant's statements about miscarriages or stillbirths have been used without question, although by some definitions a few of the miscarriages might be termed stillbirths.

Tables 2 and 3 indicate the pregnancy wastage in the consanguineous and control families, respectively. The families listed above the stepped line are those in which all pregnancies have resulted in live births. Seventeen consanguineously married women have not had any pregnancies, 68 have had a liveborn child at each pregnancy, and 24 have lost one or more pregnancies. All pregnancy losses were miscarriages except for three stillbirths. One woman had five pregnancies of which one was a live birth, one a stillbirth, and three were miscarriages, and one woman had one liveborn child and two stillbirths. Among the controls, 11 women have had no

TABLE 2. THE NUMBER OF PREGNANCIES AND LIVE BIRTHS AMONG THE CONSANGUINEOUS FAMILIES

Live births \ Pregnancies	0	1	2	3	4	5	6	7
6							—	1
5						4	1	3
4					2	2	1	—
3				11	5	—	—	—
2			31	2	2	—	1	—
1		20	1	1	—	1	—	—
0	17	2	—	1	—	—	—	—

TABLE 3. THE NUMBER OF PREGNANCIES AND LIVE BIRTHS AMONG THE CONTROL FAMILIES

Live births \ Pregnancies	0	1	2	3	4	5	6	7	8	9	10	11
8									—	—	—	1
7								—	—	—	—	—
6							—	2	—	—	—	—
5						—	1	—	—	—	—	—
4					5	1	—	—	—	—	—	—
3				8	3	1	—	—	—	—	—	—
2			28	3	1	—	1	—	—	—	—	—
1		12	3	1	—	—	—	—	—	—	—	—
0	11	1	—	—	—	—	—	—	—	—	—	—

pregnancies, 53 have had a live birth at each pregnancy, and 19 have lost one or more pregnancies. Of the lost pregnancies, a stillbirth occurred to one of the women who lost one of two pregnancies. For one of the women who lost one of seven pregnancies, the loss was of a stillborn child, twin to a premature infant who died soon after birth.

The frequency of families in which the female has never been pregnant is .1560 (17/109) among the consanguineous and .1325 (11/83) among the controls. These frequencies do not differ significantly. However, the analysis of the data is improved by considering only those childless marriages for which the length of marriage has been sufficient to show that children are not likely to occur. Although 15 of the sterile consanguineous couples have been married and remained together for ten or more years, only five of the sterile control couples have been married this long. Correcting for the incompletely observed couples, 15 of 107 consanguineous couples have not had any pregnancies, whereas only 5 of 77 control couples have not had any pregnancies. This difference is not significant ($\chi^2 = 1.90$, 1 d.f., $P > .05$. All χ^2 tests with one degree of freedom have been corrected for continuity). Many of the parents stated that they had heard that consanguinity has deleterious effects on the children. The extent to which these beliefs may have affected the fertility of these families is unknown. Most of the sterile families have expressed great regret over their sterility.

It is possible that the sterility observed has been conditioned by the age at mar-

riage. As previously noted, a number of marriages have been omitted from consideration because of the age of the contracting parties. These have included all sterile marriages in which the wife was at least 36 years old at the time of marriage. Also omitted was one marriage in which the husband was described as too old to have children. Even though these cases had been removed, the median age at marriage of the sterile women was about two years greater in each group than the median age at marriage of those women who have become pregnant. These differences are not significant.

A small bias toward early marriage is effected by the marriage of women who become pregnant prior to marriage. The marriage and birth data in the county-records control may aid in understanding the magnitude of the effect of premarital pregnancy on marriage fertility. In seven of the 133 cases, a child was born within the first seven months of marriage. This suggests that for the population being studied in this paper the frequency of pregnancy at the time of marriage is of the order of five per cent. This could account for only a small difference between fertile and sterile women in age at marriage. Furthermore, the small number of sterile women dealt with in this report does not indicate with any certainty that the apparent lateness of their marriage is other than a chance deviation.

Twenty-three of the consanguineous women have had a total of 36 miscarriages. Thus .2500 of the 92 fertile women have had one or more miscarriages and .1452 of the total of 248 pregnancies have resulted in miscarriage. There have been 25 miscarriages among a total of 17 control women. This gives one or more miscarriages among .2361 of the 72 fertile women and .1289 of the total of 194 pregnancies have ended in miscarriage. By both criteria the differences are slightly in favor of the control women, but are not significant. *If* there is a correlation between miscarriage frequency and age, the slightly greater age at marriage of the consanguineous women might account for the differences observed. The woman's statement as to the approximate age of the fetus at the time of the miscarriage has been used in the compilation of table 4.

The three stillbirths observed among the consanguineous families do not differ significantly from the two stillbirths observed among the control families.

We have previously suggested that the existence of very early fetal deaths could profitably be looked for in investigations into consanguineous marriages (Slatis and Reis, 1956). If there is a class of lethal genes which acts so soon after conception that the fact of conception is not even recognized, this might be observed as a delay in the average time between marriage and the birth of the first child or as an increase in the interval between the births of two children of adjacent birth rank. Because of the difficulty of gathering information on the pregnancies resulting in other than liveborn children, only live births have been considered. For firstborn children, correction must be made by the omission of those born before the eighth

TABLE 4. LENGTH OF GESTATION OF MISCARRIAGES

Months.....	1	2	3	4	5	6	7	Unknown	Total
Consanguineous	2	8	17	4	1	1	2	1	36
Controls	5	5	9	3	—	2	—	1	25

month of marriage. Among the consanguineous families, adequate data exist for 71 firstborn children. The median time to first birth is 17.7 months. Sixty-five control families can be used for this study. The median time to first birth is 23.7 months. These values cannot be considered as differing significantly. It should be noted that, contrary to expectation, the consanguineous group had the shorter median time to first birth. In the county-records control, the 126 qualifying families showed a median of 21.5 months between marriage and the birth of their first child. This interval is between the values observed for the two interviewed groups.

The difficulties associated with establishing the date of marriage do not exist for the time interval between the birth of the first and the second child. The 64 consanguineous families supplying adequate data show 27.5 months between the first two liveborn children, whereas among the 55 related controls the first two children are separated by an interval of 36.5 months. Here again, the difference is not great enough to be considered as other than chance variation and it is in the direction contrary to that expected. Thus, the search for early lethals is negative.

Liveborn children

The consanguineous couples have had a total of 209 liveborn children of which 107 have been boys and 102 girls. The 167 liveborn control children include 90 boys and 77 girls. The sex ratio in the two groups is very similar ($\chi^2 = .17$, 1 d.f., $P > .05$) and there is no significant difference from the usually reported sex ratio for a U. S. white population (51.5 per cent boys). The numbers of children per fertile family are almost identical, being 2.27 for the consanguineous and 2.32 for the controls (note that many families are not yet complete, so that the true family size may be somewhat greater).

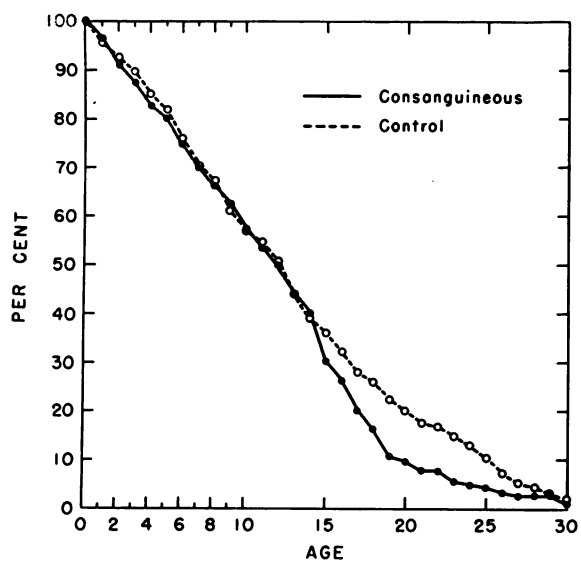

FIG. 2. The percentage of living consanguineous and control children who exceeded a given age at the time of interview.

Figure 2 is a representation of the age of the living children at the time of interview. A cumulative graph has been used so that the proportion of children that are as great or greater than any given age may be read directly (e.g., about 70 per cent of the children in each group are seven years old or older). Up to the age of 14, the two curves agree very well. Thus, for conditions with an age of onset less than 14, the proportion of each group that has passed through this period is the same. About one-third of the consanguineous marriages took place between 1936 and 1938, and because of this, about 30 per cent of the consanguineous children were between their 14th and 19th birthdays at the time of interview. The control families, having married a bit before or a bit later than their sibs, have their children more evenly spaced in this period. Since almost no observation in this paper is dependent upon conditions with an age of onset greater than the 14th birthday, this difference is of little consequence. The difference indicates, however, that a greater percentage of the control children was born over 20 years ago, and, to the extent that medical techniques were improving during that period, the control children experienced a slightly greater risk of childhood death than did the consanguineous children.

Infantile and childhood death

Seventeen of the consanguineous children have died. Four died within the first week of life and the other 13 died at various ages up to ten years. None of these deaths has been attributed to accidental causes other than injury at birth. In addition, one consanguineous child is known to have died after the interview (age 20). Death was attributed to a brain hemorrhage, and a minor injury received several years earlier has been implicated as a contributory factor. This death is not included in this study. Only four of the control children have died, three on the day of birth and one at the age of one year.

These deaths are listed in table 5. Death certificates were sought for all of them and were found for those noted by a check mark. A further check mark indicates than an autopsy was recorded on the death certificate. In those cases for which a death certificate was observed, the remarks are based on its statements except where otherwise noted. Except for the neonatal deaths, the age at death is not accurately known if the death certificate was not found.

The case of cystic fibrosis and von Gierke's disease (glycogen storage disease of the liver) are attributable to the action of recessive genes. The sixth child in family 11 died of a condition described as muscular dystrophy. Although the autopsy record for the fifth child makes no mention of this condition, it is possible that the first, fifth, and sixth children in family 11 died because of homozygosity for the same gene. It is likely that other deaths were also due to the effect of specific recessive genes, but this is not ascertainable at this time.

The observed difference in death rate, 17 among 209 live births as opposed to 4 among 167, is significant ($\chi^2 = 4.76$, 1 d.f., $P < .05$). In addition to this, one of the consanguineous children is moribund, as will be noted later, so that the frequency of death in this group is certain to go even higher. The fact that the 17 observed deaths represent only 12 families may be indicative of non-randomness with respect to mortality. Non-randomness of this type would be expected on genetic grounds,

TABLE 5. DEATHS OF LIVEBORN CHILDREN

Consanguinity	Family	Live births	Miscarriages	Stillbirths	Birth rank	Sex	Death certificate	Autopsy	Age			Year of death	Cause of death stated on the death certificate, and remarks
									Years	Months	Days		
+	1	2	0	0	1	F	√	—	0	1	1	1951	Peritonitis due to bowel obstruction and adhesions. Surgery per formed.
+	2	2	0	0	1	F	√	—	5	5	4	1956	Cardiac failure due to cystic fibrosis, pancreatic and pulmonary.
					2	F	—	—	2	6	—	1954	Parents state child had cerebral palsy as a result of birth injury.
+	3	2	0	0	1	F	√	√	0	9	19	1949	Pertussis, bronchopneumonia, diarrhea.
+	4	3	1	0	2	F	√	√	0	0	1	1950	Congenital pulmonary atelectasis. Parents state infant had harelip; premature.
					3	M	√	√	0	5	3	1953	Bronchopenumonia. Parents state infant was spastic.
+	5	4	0	0	4	M	√	—	0	0	4	1956	Inanition and cachexia. Premature. No malformations.
+	6	4	2	0	1	F	√	√	1	5	25	1925	Left lobar pneumonia. Contributory: myocarditis.
+	7	5	0	0	1	M	√	—	2	9	0	1941	Cardiac failure due to marasmus due to congenital glandular dystrophy. Operations for congenital cataract. Parents state child did not speak.
+	8	2	0	0	1	M	—	—	0	0	1	1938	Parents state there was a brain injury at birth.
+	9	5	0	0	3	M	√	√	0	1	4	1947	Inanition due to von Gierke's disease involving liver, kidney and heart.
+	10	5	1	0	1	F	√	—	3	1	9	1941	Bronchopneumonia due to measles.
+	11	6	1	0	1	F	—	—	1	—	—	1939	Parents state child had convulsions and that all teeth erupted simultaneously.
					2	M	√	—	10	1	5	1950	Organic heart disease of five hours duration.
					5	F	√	√	0	9	28	1949	Bronchopneumonia.
					6	F	√	—	0	7	12	1956	Muscular dystrophy. Parents state convulsions occurred.
+	12	2	0	0	2	F	√	√	0	0	4	1943	Fusion of pulmonary artery and aorta; interventricular septum defect; large patent foramen ovale.
—	13	2	0	0	2	F	√	—	0	0	0	1946	Intracranial hemorrhage (birth injury).
—	14	4	0	0	2	M	—	—	0	0	0	1940	Cause not known.
—	15	6	0	1	3	F	√	—	0	0	0	1946	Premature, placenta partialis. Parents state infant was twin to a stillborn male.
—	16	2	0	0	2	M	√	—	0	11	22	1939	Bronchopneumonia following a cold and bronchitis.

but an adequate analysis of it awaits a greater number of cases. There is, to some extent, a self-augmenting feature in this non-randomness, since early deaths may play a role in bringing forth more children as replacements (see, for example, Glass, 1950). Thus, the last child in family 11 was born after the deaths of three of her sibs, and it may be relevant that this, the consanguineous family with the largest number of liveborn children (six), has never had more than four living children at any time. Also, the frequency of death among the consanguineous families having four or five liveborn children is greater than among the smaller families.

The male:female ratio of 6:11 among the dead consanguineous children does not differ significantly from 1:1. As will be seen among children with serious ailments it is the boys who are more frequently affected.

Abnormalities and ailments

The various infrequently occurring abnormalities and ailments of the living children have been listed in tables 6 and 7. Thirty-one of the consanguineous children are listed (no child is listed twice), but only 16 of the control children have been found to have complaints of a similar nature ($\chi^2 = 2.55$, 1 d.f., $P > .05$, not significant). The male:female ratio is 23:8 for the consanguineous and 9:7 for the controls. If the listing had been limited to those children whose abnormalities have seriously interfered with the processes of a normal life, eight of the consanguineous children (all boys) would be included but none of the controls ($P = .007$ by Fisher's exact method, significant, that a deviation of this magnitude will be found in this direction). The tables are divided into (1) ailments requiring special care over a long period of time, (2) less serious ailments, and (3) uncommon infections and their sequelae. Only the last two categories occur among the control children. Except for the child who is deaf, there is little evidence concerning the recessive nature of the ailments. This listing may, however, in conjunction with others, prove useful in establishing the role of recessive inheritance of certain of these ailments. Even in the case of the deaf child there is the possibility that the other conditions that he displays may be pleiotropic effects of the gene responsible for the deafness.

The similarity of available medical treatment may be investigated by a determination of the frequency of more routine medical procedures. Among the living consanguineous children, 76 have had tonsillectomies, 3 have had appendectomies, and 10 others have had both of these operations (40, 2, and 5 per cent, respectively). Among the controls, these values are 69, 6, and 7 (42, 4, and 4 per cent, respectively). These operations have been slightly more frequent among the controls. The differences are not statistically significant. The only unusual occurrence among these cases is that a (living) female in family 11 (see table 5) is noted as having had double pneumonia after her appendectomy at age 7 weeks.

When the incidence of broken bones was used as an impartial index of accidental occurrences, inquiry revealed that 13 of the consanguineous children have each had one fracture; nine of the control children have had a single fracture and one additional control has had three fractures. Thus, children with broken bones occur in almost the exact ratio as the numbers of the two classes of children. No case of unusual bone fragility has been observed.

TABLE 6. AILMENTS AND ABNORMALITIES OF CONSANGUINEOUS LIVING CHILDREN

	M	F	Complaint
	1		Hydrocephaly (age 3, not expected to survive longer).
	1		Deaf. Also has hernia; an undescended testis.
	1		Blind (infectious etiology?)
	1		Poor heart and respiratory function (in a nursing home).
	1		Mentally retarded.
	2		Cerebral palsy and leg abnormalities (brothers, there are indications that Rh incompatability was responsible).
	1		Rheumatic fever (severe case with frequent hospitalization).
	1		Bilaterial hernia.
		1	Hernia.
		1	Cleft palate.
	1		Defective hearing.
	1		Enlarged thymus (fed intravenously for a period).
	1		Pyloric spasm (?)
	1		Pityriasis rubra pilaris.
	1		Osgood-Schlatter disease.
		1	Nervous eczema (neurodermatitis?).
		1	Partial removal of a kidney.
	1		Convulsions in infancy.
	1		Mastoid operation.
		1	Rheumatic fever.
	4	3	Pneumonia (two males have also had convulsions).
	2		Polio (one child now has an abnormal spinal curvature).
	1		Spinal meningitis.
Total	23	8	

TABLE 7. AILMENTS AND ABNORMALITIES OF CONTROL LIVING CHILDREN

	M	F	Complaint
	1		Congenital pilonidal cyst.
	1		Gall bladder disease.
		1	Cleft palate.
		1	Congenital cataract.
	2		Hernia.
	1		"Cysts on chest."
	1		"Gland trouble in the neck."
		1	Nervous eczema (neurodermatitis?).
		1	Defective eye muscle.
		1	Psoriasis.
	2		Pneumonia (one of these children was affected twice).
		1	Mastoid operation.
	1		Polio.
		1	Spinal meningitis.
Total	9	7	

With minor exceptions, schooling is essentially a function of age up to about the age of 16. Official school records have not been obtained for these children. Of the 21 consanguineous children who have reached the age of 19 (which is a convenient age for ascertaining the likelihood that higher education will be pursued), five have

taken some college work. Of the 36 control children aged 19 or greater, 15 have had some college work. The difference between the two groups is not significant ($\chi^2 = 1.15$, 1 d.f., $P > .05$).

A number of the older children are married, but no analysis of the number of their offspring has been made. Few of them have been married any length of time.

The three families which have a greater degree of consanguinity than that of first cousins have not contributed to the abnormalities observed among the consanguineous children. The aunt-nephew marriage has been sterile. The three children of the double first cousins are all less than six years of age and have not had any recorded medical treatment. The uncle-niece family has had one miscarriage and four live-born children. Their only recorded medical treatment is that three of the children have had tonsillectomies.

DISCUSSION

In this comparison between the consanguineous and control groups the major questions are the fertility of these marriages, the viability of the fetuses, and the viability and health of the children. Some doubt exists about the possibility of a mechanism that could cause the sterility of a consanguineous couple. Common heterozygosity for a large number of early-acting recessive lethal genes would easily account for this phenomenon, but this would suggest that most consanguineous couples should have difficulties in conceiving. On the contrary, the median times to first and second births are less than those of the controls. Schull (1958) has investigated the time to first birth for consanguineous couples in a large Japanese sample and he too finds little or no effect on the time to first birth. Nevertheless, our data suggest that the frequency of sterility may be higher among consanguineous couples. Also Remlinger and Coen (1947) have reported a high frequency of sterility in closely consanguineous marriages among Moroccan Jews, and Sutter and Tabah (1952) found a slightly elevated frequency of sterility among the consanguineous couples in their study of French Catholics. Thus, the existence of early-acting recessive lethal genes in the population, as deduced from observations on sterility and time to first birth, is still open to question.

With respect to miscarriages and stillbirths, the numbers observed in the two groups are so similar that there seems to be little, if any, effect of consanguinity on these conditions. Thus, for all stages from conception to live birth, there may not be any effect of consanguinity. This fact is important for the understanding of the time of action of deleterious genes.

The relatively equal viability up to the time of live birth soon changes for the worse among the consanguineous children. It is a frequent observation that some types of abnormality are increased among the children of consanguineous marriages. The relative frequency of abnormality that has appeared thus far in this study has been high. The death rate during childhood has already exceeded eight per cent, which is very high for the population of the Chicago area for the period of time under consideration. Also, the frequency of serious abnormalities among the living children is well above the usual level for this area. On the other hand, the controls

appear to reflect the level of death and abnormality expected in the general population.

A number of papers have recently discussed the calculation of the number of abnormal recessive genes in an average person using data derived from the study of consanguineous marriages. Slatis (1954) derived a formula that takes into account the small size of families, so that a correction is made for the chance that a couple will have a recessive gene in common but will not show it among their progeny. He derived a value of eight as the average number of abnormal recessive genes carried heterozygously per person, but the data were admittedly biased in favor of a high rate. Böök (1957) has used a different method, which is based on the same principles, and arrived at an estimate of three detrimental recessive genes per person in a North Swedish population. Böök's method makes two unusual assumptions: (1) that among families showing at least one recessive mutant, no further information is derived from the family size or the number of mutants segregating, and (2) that miscarriages and stillborn children are normal.

By subtracting the wasted pregnancies and by using Slatis' formula, which takes into account the number of separate mutant genes observed in each family, one finds that Böök's data give an average value of 5.32 detrimental mutant genes per person. Penrose (1957) has also analyzed Böök's data, correcting them to eliminate the miscarriages and stillbirths. His method is satisfactory in large samples, though it will be less accurate than Slatis' method in these small samples. Penrose suggested that the number of deleterious genes observed among the children of first cousins would reflect $\frac{1}{16}$ of the number present heterozygously in the average common great-grandparent, but this value should be $\frac{1}{32}$. Therefore, Penrose's calculation of 2.94 deleterious genes (16 times the frequency of individuals homozygous for a deleterious gene) should be doubled to 5.88, which is reasonably close to the value calculated by Slatis' method. These values for Böök's data are only about one standard error below Slatis' calculation of 8.0 ± 2.6.

Morton, Crow and Muller (1956) have advanced the concept of lethal equivalents, which is more sophisticated than the concepts of simple recessivity previously employed. Their estimates of the number of lethal equivalents are derived by assuming that the difference in death rate between the consanguineous and control populations is an expression of lethal genes of various degrees of penetrance. In data such as ours in which the observations are (essentially) limited to controls and a single type of consanguinity, simple mathematical procedures may be used. As observed above, for data on first cousins, the homozygous recessive genes reflect $\frac{1}{32}$ of those present in an average common ancestor. Therefore, the number of lethal equivalents carried by an average individual may be found by multiplying by 32 the difference: (frequency of death among the consanguineous children) − (frequency of death among the control children). For our data, this method is similar to that of Penrose, but it includes a correction for the mortality observed among the controls. It yields a measure of the sum of the number of rare lethal and semilethal genes times their penetrances, rather than of the number of loci at which a lethal gene occurs.

It should be stressed that the observed differences in miscarriage and stillbirth

rates in our data are far too small to have any importance attached to them. They are, however, in the direction expected on the theory that they are caused by recessive lethals, and a value representing the indicated number of lethal equivalents can be calculated. The controls, having lost .1289 of their pregnancies through miscarriage, show .0163 fewer losses than the .1452 shown by the consanguineous group. Multiplied by 32, the indicated number of lethal equivalents in the average person that would act in this period of development is .52. Stillbirths show a difference of .0024, or .08 lethal equivalent. Neonatal deaths (deaths within the first month of life, which is the definition used by Sutter and Tabah, 1952, whose data are analyzed by Morton, Crow and Muller) show a difference of .0011, which indicates the action of .03 lethal equivalent. This total of .11 for the lethal equivalents for stillbirths and neonatal deaths is only a small fraction of the number calculated by Morton, Crow and Muller, and even if part of the miscarriage rate should be included, it would still be extremely low. The reader is referred to the discussion by Morton, Crow and Muller for remarks pertinent to the "relaxation of selection under modern conditions" which probably is indicated by our low perinatal mortality. Infantile and juvenile deaths occurred in our study to .0061 of the control children and .0634 of the consanguineous children, which gives a difference of .0573 and an indication of 1.83 lethal equivalents. The total number of lethal equivalents from early miscarriage through the juvenile period is thus 2.46.

Parallel with the concept of lethal equivalents is that of abnormal equivalents, the number of fully penetrant genes that would give the observed increase in abnormalities. The abnormalities listed in tables 6 and 7 occur in 31/192, or .1615 of the consanguineous children and 16/163, or .0982 of the control children. If due to the effect of consanguinity, this difference, .0633, indicates the presence of 2.03 abnormal gene equivalents.

As seen in table 8, the consanguineous families and the control families appear to differ because of the action of a total of 4.49 detrimental gene equivalents. These were carried by the average great-grandparent of the consanguineous children and, subject to the errors inherent in our methods, this would approximate the average number carried by the members of our contemporary society. The failure to observe all of the children through the entire juvenile period could be construed as indicating that this value is, to a slight extent, an underestimate. The relaxation of selection

TABLE 8. LETHAL AND ABNORMAL EQUIVALENTS AT VARIOUS STAGES IN THE LIVES OF CONSANGUINEOUS AND CONTROL CHILDREN

Stage	Consanguineous			Control			Difference	Difference × 32 = no. of equivalents
	Affected	Total	Frequency	Affected	Total	Frequency		
Miscarriage	36	248	.1452	25	194	.1289	.0163	.52
Stillbirth	3	212	.0142	2	169	.0118	.0024	.08
Neonatal death	4	209	.0191	3	167	.0180	.0011	.03
Infantile and juvenile death	13	205	.0634	1	164	.0061	.0573	1.83
Abnormality	31	192	.1615	16	163	.0982	.0633	2.03
Total								4.49

to which we have referred would suggest that this difference was even greater only a generation or two ago. It should be noted that because of incomplete penetrance the estimate of the number of lethal equivalents plus abnormal equivalents will give a smaller value than the actual number of loci involved.

It has been hoped that the results of this study could be used to estimate the added risk of harm to the children in a consanguineous marriage. The *indicated* increased probability of loss through stillbirth is .0024, through neonatal death is .0011, and through infantile and juvenile death is .0573. The added risk of sickness or abnormality is indicated to be .0633. These values suggest that, in the society studied, there is an added risk such that an additional 12 per cent of the children of consanguineous couples will be affected over the percent affected among outbred children. The controls have shown a very low rate of death, which sociologically is one of the most severe of these conditions, and the indication is that the death of children is three times as great among consanguineous families as among controls, i.e., 17 of 209 consanguineous children as compared to 4 of 167 control children. The rate of all abnormalities, as defined by tables 6 and 7, is less than twice as great among the consanguineous children, but if only major abnormalities are considered, the added risk of consanguinity is exceedingly great, i.e., 8 of 192 living consanguineous children have had serious abnormalities, whereas 0 of 163 living control children have suffered serious abnormalities.

SUMMARY

A study has been made of 109 consanguineous marriages in the Chicago area, of 83 control marriages, and of a few aspects of 133 other control marriages. The consanguineous marriages give some evidence for a greater frequency of sterility and of childhood death and childhood abnormality. The loss of children through miscarriage and stillbirth was not significantly higher, and there is no evidence that rare recessive lethal genes cause the loss of newly fertilized zygotes. Subject to the errors inherent in our methods, the indicated number of lethal equivalents per person is 2.46, and 2.03 abnormal equivalents are also found. Thus, the average person may be carrying the equivalent of 4.49 fully penetrant genes which cause detrimental effects in a modern American population. To some extent these values are underestimates for the population studied, and the ancestors of this population under more primitive conditions probably expressed the lethality and abnormality of many additional genes. The rate of death among the consanguineous children is three times that of the controls and their rate of abnormality is also greatly increased, the amount of the increase being dependent upon the definition of abnormality.

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