APPENDIX III

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The Incidence of Consanguinity in Japan, with Remarks on the Utilization of this Data in the Estimation of Comparative Gene Frequencies and the Expected Rate of Appearance of Induced Recessive Mutations.[1]

by

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Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

The frequency of occurence of consanguineous marriage has been rather extensively investigated in European populations. There exists, however, relatively little exact data for other parts of the world. The following studies were undertaken in an attempt to supply information on this point for one type of Mongolian population, namely, Japanese residing on the islands of Honshu and Kyushu.

Investigations of this type were formerly of interest primarily to the social anthropologist. More recently, students of human genetics have realized the significance of this information for the solution of certain of their problems. The authors have been particularly interested in the light such data might throw on two questions, namely, 1) the rate with which any recessive mutations induced by the atomic bombings of Hiroshima and Nagasaki might be expected to appear in the descendants of the survivors, and 2) the comparative frequencies of certain inherited traits in Caucasian (European) and Mongolian (Japanese) populations.

THE DATA

The data which we have collected on the incidence of consanguinity in Japan fall into two different categories.

A. Pregnancy Registration Results

During the period covered by this investigation (1948-1949), a system of voluntary pregnancy registration was in force throughout Japan. As soon as the fifth month had been reached, a pregnant woman was entitled upon registration to receive certain rationed items. Because of the economic stringencies obtaining in Japan during this period, registration was relatively complete. In connection with an attempt to investigate the potential genetic effects of the atomic bomb, there has been superimposed upon this system of pregnancy registration a special questionnaire in Hiroshima and Nagasaki, and in a control city, Kure. This special questionnaire includes an item concerning consanguinity. In point of size, these towns are respectively the fifteenth, nineteenth, and twenty-second largest in Japan, having on the basis of the 1947 census populations of 224,100, 198,642, and 185,740, and the results secured in these localities may be regarded as more or less typical of the cities of Southern Japan. All registration clerks have been carefully schooled concerning the various degrees of consanguinity and the manner in which to elicit information on this point. Thus far a total of 23,804 questionnaires have been completed. The results are given in table 1. Of the women registering, 93.5 per cent were between the ages of 20 and 39; these results therefore tend to reflect the situation with respect to marriages contracted between 1929 and 1948.

In connection with the above-mentioned genetic studies, it has been customary, upon the report of the termination of certain of these pregnancies, to make a follow-up visit to the home of the woman in question. On the occasion of that visit, the question of consanguinity was again raised; the interviewer was not aware of the nature of the previous statement. Out of a total of 1,681 women so interviewed, 22 failed to confirm their previous statements concerning consanguinity, or stated a degree of relationship other than that previously obtained. This is a significant discrepancy. No particular trend was evident, i.e., in eight instances women who had previously stated that consanguinity

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

existed now admitted to no such relationship, in six cases the reverse was true, while in eight other cases the degree of relationship was otherwise than originally stated. To what extent the second statement represents the result of further inquiry into the matter and hence is more accurate, is not clear. If we assume that all women who have on either of the two occasions stated that theirs was a consanguineous marriage are, in fact, related to their husbands, then the overall incidence of consanguinity would be about 0.36% higher.

B. Special Survey Results

The consanguinity data obtained from the genetic questionnaires were of such interest that several special surveys were undertaken in an attempt to secure a more rounded picture of the situation. A sector of Hiroshima (the Hijiyama district) was selected as more or less typical of the city as a whole, and an attempt was made to obtain a statement from each married couple in that sector concerning consanguinity. A similar procedure was carried out in Kure (the Katayama district). This procedure yielded a wider age distribution than the previous study, making possible an analysis of the data for secular trends. In addition, two special areas located near Kure were studied. The first of these (Midori Machi) is situated on the outskirts of Kure and was of special interest because it is an Eta village. For centuries those persons in Japan who work with the flesh or its products (e.g., butchers, leather workers) have tended to be isolated socially from the rest of the population, corresponding in a sense to India's untouchables. These persons are known as Etas. They have aggregated into special villages or sections of the larger towns. It was the impression of the Japanese Nationals with whom we talked in the planning of this investigation that the incidence of consanguinity was especially high in such communities. The second area selected for special study was a fishing community (Dainu) located some six miles from Kure, with a population of 1,787. Except for its proximity to a large city, this settlement may be regarded as more or less typical of the smaller agricultural and fishing villages of Southern Honshu, the main island of Japan.

The results are shown in tables 2 and 3. Minor discrepancies in percentages and totals between the two tables are related to the inability to obtain accurate ages in some cases where a spouse was deceased or divorced, and the consequent necessity of omitting some persons from table 3 who are represented in table 2. The rate of consanguinity observed in Kure and Hiroshima by this approach (table 2) agrees well with that seen in the previous study. Consanguinity rates appear to be higher in the smaller communities, although because of the numbers involved the differences are not significant. It is noteworthy that the consanguinity rates in the Eta village under consideration were not higher than those of a fishing village of somewhat larger size. In all four of the communities studied the affinity rate, as measured by the frequency of "in-law" marriages, is quite high. This is an understandable corollary of a high consanguinity rate. Table 3 reveals no significant tendency for consanguinity rates to have altered in the past sixty years, although first cousin marriages may have been somewhat more common among the older individuals.

The two smaller communities studied were actually relatively accessible. The question naturally arose as to what the consanguinity rates might be in some of the smaller but less accessible coastal and interior villages. At our suggestion, Dr. F. Kida and associates of Kumamoto University undertook a

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

rather extensive survey of some of the towns and villages of the island of Kyushu, Japan. Their results, which have been reported elsewhere (Kida, Kanokogi, and Kojima, 1949), are shown in table 4. The communities investigated have been classifiedas cities (only one - Kumamoto city - population 245,841), towns (population 6,981 to 13,149), and villages (population 1,818 to 4,352). The consanguinity rates encountered in some of these villages are as high as any we have found recorded in the literature.

THE UTILIZATION OF THESE DATA IN VARIOUS CALCULATIONS

The magnitude of the consanguinity rates encountered in this study may best be appreciated by a reference to table 5, which summarizes the findings with respect to consanguinity in a number of European populations. Although certain isolated European communities exhibit rates comparable to those encountered in Japan, there has to date been recorded no major population or geographical unit with rates of this magnitude. The integration of the Kure and Hiroshima data on consanguinity into a single figure may be accomplished through the use of the coefficient of inbreeding, α (Haldane and Moshinsky, 1939). For the most extensive European data available, those of Orel (1932) on the archdiocese of Vienna, the observed α approximates 0.00060. For our Japanese data on urban populations, the observed α in women registering pregnancies for ration purposes approximates 0.00372. Both figures are of course an underestimate, since individuals are undoubtedly not uncommonly unaware of even relatively recent and close consanguinity, and further, because of the relatively rapid expansion of the world's population, remote consanguinity must be involved in a sizeable fraction of marriages. Taken at face value, however, these figures indicate a degree of inbreeding in the Japanese which is about six times that observed in a roughly comparable European population. In the European data, 72% of the known value of α was contributed by first cousin marriages; in the Japanese data, 78% of the known value is due to marriages of this type.

Two general groups of factors operate in the production of high consanguinity rates, namely, geographical and social, including in the latter category both localized social pressures and social customs. Factors of the former type are primarily responsible for the findings of Nöllenburg (1932) Egenter (1934), and Böök (1948) with respect to small and isolated German, Swiss, and Swedish communities, while factors of the latter type account for the consanguinity rates sometimes observed among members of Jewish groups (Reutlinger, 1923) or the Fiji Islanders (Pearson, 1911). It seems probable that in Japan both these types of factors are at work. Although Japan is a small and heavily populated country, it is our impression that there is a considerable degree of relative isolation between its various villages, especially those in the interior, with - at least prior to the disruptions of the war - a less mobile population than is true of many other countries. A more important contributing factor than this is to be found in the social structure of the country. There is, to begin with, a relatively rigid stratification, with, for the most part, opportunities for marriage only within one's stratum. On top of this, marriage in Japan is still guided to a great extent by parental wishes. Parents, wishing to conserve the family assets, and being reluctant to underwrite the risks involved in the selection of a marriage partner who is a relatively unknown quality, will understandably often choose from within the family circle.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Dahlberg (1948) has presented formulae for calculating the size of the isolates into which a population is subdivided on the basis of the frequency of cousin marriages. Such formulae assume that cousin marriages are contracted at random, and therefore obviously cannot be used to calculate isolate size in Japan.

The estimation of gene frequencies

A genetically satisfactory evaluation of anthropological differences is possible only in terms of the relative frequencies of specific genes and their interaction with local environmental factors. Thus far, this type of evaluation has been feasible only for certain rather common genes of comparatively little adaptive significance, such as those responsible for the A-B-O, M-N, and Rh blood types, color blindness, and the ability to taste phenylthiocarbamide (review in Snyder, 1947). A further step would consist in a comparison of the frequency of various recessive traits with a considerable selective disadvantage. Direct surveys of the necessary magnitude have not yet been carried out. However, there is an indirect approach to the problem. The frequency of a given recessive gene may be calculated if the incidence of first cousin marriages in the general population and among the parents of affected individuals is known, and if one assumes panmixia. Formulae suitable for this calculation have been proposed by Lenz (1919), Weinberg (1920), Dahlberg (1938, 1948), and Hogben (1946), among others; these all yield approximately the same result but that proposed by Weinberg and Dahlberg is perhaps preferable, namely,

$$k = \frac{c}{c + \dfrac{16(1-c)q}{1 + 15q}}$$

or, restated in terms of q,

$$q = \frac{c\,(1-k)}{16k - 15c - ck}$$

where q = the frequency of the recessive gene responsible for the trait in question,
k = the proportion of first cousin marriages among the parents of affected persons, and
c = the proportion of first cousin marriages among the population as a whole.

The relationships of q, c, and k are graphically illustrated in figure 1. As we shall see below, figure 1 allows for an estimation of gene frequencies which is certainly as accurate as the data justify.

The use of this formula is subject to very severe limitations, some of which have been clearly stated in the past and some of which have not. Dahlberg (1938, 1948) has in particular pointed out the mathematical pitfalls inherent in the use of this equation. Human populations of any magnitude are not in a state of panmixia, but are broken up into isolates of greater or

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

lesser degree within which there occur significant variations in gene frequency. Although it is clear that the occurrence of these isolates may in specific instances invalidate the use of this formula where extreme accuracy is desired, it is not yet apparent to what extent the formula may be relied on for a serviceable approximation to gene frequencies. It is certain that the concept of complete isolates is as spurious as the concept of panmixia--over a period of years there is a very substantial gene exchange between neighboring communities. However, at the present time the coefficients of migration and interchange cannot even be approximated for the sub-groups comprising any sizeable human population. Accordingly, while there can be no doubt of the theoretical importance of isolates, there is no human population whose breeding structure is sufficiently well known to enable us to estimate the inaccuracies introduced by isolate effects. In the present case, we are not so much interested in absolute values as in comparative values; the formula may have greater validity in this latter context. This question, of the appropriateness of using the equation given above for a first approach to the problem, will be returned to after we have considered the biological shortcomings of the data.

In addition to purely mathematical pitfalls, there are many biological complications standing in the way of the estimation of gene frequencies. The traits selected for consideration must always be clearly differentiated from normal, and must satisfy all the criteria for monogenic recessive inheritance. It will never be possible to be certain in man that a given recessive trait is always due to the same recessive gene. Gates (1946) has cited numerous illustrations where what to the clinician appears to be one and the same condition may have different genetic bases in different families. Thus, retinitis pigmentosa may apparently be due to an autosomal dominant or recessive or a sex-linked dominant or recessive; partial sex linkage also seems to have been established. No matter how carefully one selects diseases for consideration, one can never be certain that all cases have the same genetic basis. Furthermore, the estimation of consanguinity in the parentage of any given group of people is subject to very serious errors, both on the part of the recorder and of the persons concerned.

Despite all these well recognized theoretical factors tending to impair the accuracy of the results obtained with the equation given above, it is of interest, now that data are available concerning the incidence of consanguinity in the Japanese, to inquire into the incidence of consanguinity among the parentage of individuals with certain well defined recessive traits, and to compare the data so obtained with what is known concerning European populations. Although such an attempt has only limited validity in the light of our present information, quite aside from the tentative conclusions which may be drawn it serves an added purpose in highlighting present gaps in our knowledge of the genetics of man. Table 6 presents data concerning the comparative frequencies of five genes as calculated by this method. In the preparation of this table we have been greatly aided by Dr. R. Kawakami of the Japanese Institute of Public Health, who in the course of assembling a monograph on the genetics of the Japanese has summarized a vast amount of literature not usually available to the Occident, and has kindly made certain of his results available to us in advance of publication, and in particular where there are one or two outstanding studies on which reliance can be placed, made these known to us. We have also used, for purposes of comparison, Komai's two summaries (1934, 1947).

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

As will be apparent below, the data on the incidence of consanguinity among the parentage of individuals with various recessive traits is quite unsatisfactory. In the table there is indicated a range within which the true value of k may lie. This range is obtained in the following manner. For each trait, a minimum and maximum k value can usually be estimated from the literature. The "true" value lies someplace between these two; for each trait an attempt has been made to estimate this true value. A standard error has then been calculated, using as n the total number of segregating sibships reported. Actually, of course, the range of error involved is greater than that given by the standard error, but for present purposes this error is a sufficient approximation. In these calculations, the c value assumed for the European population is 0.01, and for the Japanese, 0.06. The value of 0.01 is of course too high for contemporary European populations, but probably approximates the true value 40-60 years ago, when the parents of many of the sibships on which the calculations are based were married. Although the observed incidence of first cousin marriage in our two studies of Japanese material was 4.30% and 4.78%, these studies were very heavily weighted in favor of urban-contracted marriages. When allowance is made for this fact and for a possible secular trend, an estimate of 6.0% seems not unreasonable. In selecting for purposes of calculation values of 0.01 and 0.06 we have been perhaps unduly influenced by the findings in urban populations, but feel that in both Europe and Japan these groups probably contribute disproportionately to persons seen in large medical centers. The assumption of c values somewhat above or below 0.01 and 0.06 would of course quite significantly influence the estimate of q, a fact readily apparent from a consideration of figure 1.

A brief discussion of each of the traits listed in the table follows:

1. Complete albinism. This clear cut and striking trait has been the object of extensive genetical studies. The evidence for the similarity of the genetic basis of complete albinism in all cases has been summarized by Cockayne (1933). The data, though scanty, do not suggest that more than one autosomal gene may be involved in the appearance of complete albinism in man. This conclusion has the support of the results of extensive work with albino mammals of several species - only a single gene for complete albinism is recognized in the mouse, rat, guinea pig, and rabbit, four mammals which have been particularly studied in this respect.

The most extensive work on albinism in man is Pearson's monumental monograph (1913). Dahlberg (1938) states that the incidence of first cousin marriages among the parents of this material is 0.17. Hogben (1946), without stating the source, repeats a similar figure for consanguinity in the parentage of albinos. We have recabulated this data for all albinos recorded as of European parentage, excluding Jews, the latter because of possible genetic differences from other Europeans, and obtain, for 217 families, a figure of 0.21. In this tabulation, quite a number of European families were excluded from consideration because it was felt they had been insufficiently investigated in respect to consanguinity. The adoption of more liberal standards would of course lower the figure given above. The corresponding q value is 0.002-0.003. The most extensive and reliable Japanese study of albinism is that of Kurasima (1937). This investigator personally interviewed the parents of 21 sibships in which albinism had occurred, finding that 10 pairs were first cousins. In the Japanese material summarized by Komai (1934, 1947), the incidence of parental consanguinity of all types is only 43.7%. The discrepancy

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

is probably a reflection of incomplete ascertainment, and we shall use Kurasima's figures. The corresponding gene frequency is 0.0029 - 0.0075.

Albinism is sufficiently common and striking that numerous attempts have been made to estimate its frequency. Its incidence in Europeans has been variously placed at from 1:10,000 in Norway to 1:100,000 in Russia (cf. Pearson, 1913, for an extensive review). No one who has considered the basis for these estimates can help but be highly dissatisfied with the available figures and the validity of the alleged differences between various groups. Probably the figure adopted by Hogben (1946), of 1:20,000 for European communities, is as satisfactory as any. Assuming an α value of 0.001, this corresponds to a gene frequency of 0.0066. Kurasima's survey of Gifu prefecture revealed, for the summed population in the years 1901-1935, a total of 559 albinos in 26,685,028 persons, an approximate incidence of 1:47,000. Assuming an α value of 0.005, this corresponds to a gene frequency of 0.0028. This latter figure is in satisfactory correspondence with the Japanese value as calculated by c and k, whereas for the European figures there is a marked discrepancy. This discrepancy has been pointed out by Roberts (1932), Hogben (1946), and Gates (1946), among others, and the suggestions made that it can be explained by the existence of several different genes for albinism. An alternative explanation stems from the fact that many of the pedigrees of albinism in the literature and on which the estimate of $k = 0.21$ is based were collected during the nineteenth or early twentieth century, at which time the value of α may have been sensibly higher than the previously assumed value, approximating 0.002, with $c = 0.02$. Under these circumstances q as calculated from figure 1 would equal 0.005, while as calculated from α and an incidence of 1:20,000 it would equal 0.006. This would appear to constitute a satisfactory agreement, but would tend to throw the European figures somewhat out of line with the Japanese estimate as based on direct methods. It is possible that this latter estimate suffers from a lack of complete ascertainment - a real problem in Japan.

2. Infantile amaurotic idiocy. The question of whether the infantile and juvenile forms of amaurotic idiocy have different genetic bases or are due to the same recessive gene, whose mode of expression is very significantly altered by various modifiers, is relatively immaterial in a consideration of gene frequencies, since by treating them as separate and distinct entities we are merely effecting two estimates of the frequency of the same gene. The apparently greater incidence of amaurotic idiocy among Jews than among Gentiles is well known. Because of possible genetic differences between the two groups, as well as differences in the value of α, we have, as for albinism, restricted our consideration to Gentiles. Unfortunately, this very drastically reduces the amount of material available. Slome in 1933 tabulated 18 sibships in which amaurotic idiocy had appeared in Gentile families. In three of these consanguinity had not been ascertained. The incidence of first cousin marriage in the parentage of the remaining 15 sibships was 0.40. Among 109 Jewish sibships, consanguinity had not been ascertained in 28, with 0.16 first cousin marriages in the remainder. This would appear to point to a valid genetic difference between the two groups, especially in view of the probably higher c value for Jewish groups. The Japanese material is also quite limited. Komai's 1934 summary does not distinguish as to type of amaurotic idiocy; in the 1947 material 3 of 6 sibships segregating for infantile amaurotic idiocy are shown as the results of consanguineous matings. Katsumma, Murakami, and Takesita in an unpublished manu-

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

script have summarized the Japanese data available to them. They were able to find reports of only 12 sibships in which the disease had appeared, for two of which parental consanguinity had not been ascertained. In the remaining 10 families, the affected children were the offspring of first cousins in seven cases. There is satisfactory agreement between the gene frequency estimates in the two populations as shown in table 6.

The estimates of the incidence of consanguinity among the parents are for European populations much better for the juvenile form of amaurotic idiocy than for the infantile type discussed above (Sjögren, 1931). Unfortunately, the Japanese material on juvenile amaurotic idiocy is so extremely deficient at present as to render a comparison meaningless, Katsumma, Murakami, and Takesita being able to find reports of only four segregating sibships, two of them the result of first cousin marriages. Sjögren (1931) in his studies on a Swedish population calculated from the k value of 0.15 observed in his material, assuming a c value of 0.01, that the gene frequency was 0.0038. In an independent calculation, based on an observed frequency of infantile amaurotic idiocy of 0.000038 in Sweden, he calculated a gene frequency of 0.0062, and a corresponding frequency of the heterozygotes of 0.012. The agreement between the two approaches appeared satisfactory. He emphasized the sources of error in his calculations and the tentative nature of his conclusions, pointing out the role of isolates (Heterozygotenherde). Dahlberg (1938) has criticized these calculations severely, writing:

"A correct calculation should show that in the isolates where the gene occurs the frequency of heterozygotes is much higher than 1 per cent., whereas the number of heterozygotes as related to the entire population amounts to only a small fraction of 1 per cent".

It is unfortunate that in this rather knotty situation Dahlberg did not publish figures to support his arguments. This problem has more recently been approached by Dunn (1947). Using a slightly different formula $\left(k = \frac{c\,(1 + 15r)}{16r}\right)$ than the one given above, he first assumed panmixia with a c value of 0.01 and then calculated from Sjögren's data an overall gene frequency of 0.0044. Pointing out (as had Sjögren) the fact that the disease in Sweden tended to occur in localized areas where the effective c value during the period in question (±1875-1930) more probably approximated 0.02, he then calculated a gene frequency in these of 0.009524. The observed frequency of occurrence (about 4 per 100,000 births) could then be explained if it was assumed that about 40% of the population was grouped into aggregates with the above gene frequency, while in the remainder the gene frequency was close to zero. However, even if this is the case, the overall gene frequency in the population would approximate $\frac{(0.4 \times 0.009524) + (0.6 \times 0.0)}{1.0} =$ 0.0038, i.e., a value which is in fair agreement with Sjögren's calculations and which certainly fails to support the above quoted statement by Dahlberg.

3. Ichthyosis congenita. There are usually recognized two forms of congenital ichthyosis, namely, ichthyosis foetalis and ichthyosis congenita larvata, while a third form, ichthyosis congenita tardiva, manifests itself shortly after birth. It is uncertain as to whether these are valid distinctions from the genetic standpoint or whether, again, this is a matter of a principal determinant influenced in its manifestation by important modifiers.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Conversely, there could be several different genetic bases for each of these three categories, although there is no evidence in that direction at the present time. Most cases of ichthyosis of early infancy fall into the ichthyosis congenita larvata group. Cockayne (1933) tabulated the case reports of this latter condition which were available to him from the standpoint of parental consanguinity. Almost all these reports concerned European material. In a total of 92 sibships for which there was complete information concerning the sibships (discarding from his tabulation the two Japanese sibships reported by Matsumoto), there was no statement concerning consanguinity in 44, no known consanguinity in 19, a first cousin relationship in 22, and other consanguineous relationship in 7. The incidence of first cousin marriages thus lies someplace between 0.24 and 0.46. It would seem reasonable to assume that in some cases where there is no statement concerning consanguinity, this matter has been investigated, found negative, and overlooked in the preparation of the manuscript, i.e., although there are undoubtedly cases of first cousin marriage among the group for which there is no statement, the incidence is not so high as where the question has been specifically answered. We shall assume, somewhat arbitrarily, that the value of k is in the neighborhood of 0.35, probably falling between 0.30 and 0.40.

The Japanese data are again quite limited. Of the seven sibships pictured by Komai (1934, 1947), six are the outcome of consanguineous marriage. Yamamoto and Ishikawa (1939), in a discussion of ichthyosis in which the above mentioned classification was followed, report that of ten sibships for which information was available concerning parental consanguinity, 8 were the outcome of first cousin marriage. As shown in table 5, the corresponding gene frequency is in satisfactory agreement with the European values.

4. Congenital total color blindness. Despite the significant clinical variations in the manifestations of this trait, we shall, for purposes of calculation, regard the group as genetically homogeneous, although it is possible that total color blindness without associated ocular symptomatology falls into a separate category. The data concerning consanguinity in the parentage of European cases of total color blindness are poor. Peter (1926) in a survey of the literature to date states that there was parental consanguinity for 14 of 60 segregating sibships, but emphasizes that because of poor reporting this represents a very minimal figure. Three of the 14 consanguineous unions were marriages between first cousins; four of the 14 involved consanguinity of a degree not stated. Peter does not list the papers on which this statement is based. The lower limit of first cousin marriages in this data is thus 0.05 to 0.12. Of the 39 segregating sibships figured by Bell (1933), four are the result of a first cousin union, three of consanguineous unions stated to be other than first cousin, six of consanguineous unions the degree of which is not stated (one definitely second cousin or more remote), 12 of non-consanguineous matings, and 14 of matings for which there is no clear statement regarding consanguinity. The lowest incidence of first cousin marriage is thus 0.11 while the highest is 0.36. Göthlin (1941) states that parental consanguinity was present in 13 of 40 well studied sibships reported in recent years by himself and other authors - assuming that half of these consanguineous unions involved first cousins, this is an incidence of 0.16. Despite these discrepancies, it appears that the incidence of first cousin marriages in this material is somewhat less than in the parentage of several of the other diseases which we have discussed - for purposes of calculation we will adopt a value of 0.16, with the true value probably lying between 0.11 and 0.21.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Three Japanese summaries are worthy of mention. Hohki (1941, quoted from Gothlin) was able to locate reports of 89 cases in 44 sibships, 0.47 the offspring of first cousin unions. Hitomi (1943) in his summary listed 67 segregating sibships, with the parents definitely first cousins in 23 instances, and quite probably so in even more, since the degree of consanguinity was not always clearly stated. This is a minimum incidence of 0.34. Komai (1934, 1947) records 69.2% consanguinity in the parentage of 26 segregating sibships. A figure of 0.45 seems a not unreasonable estimate of the frequency of first cousin marriages in the parentage of these individuals, with the true values possibly between 0.39 and 0.51. There is satisfactory agreement between the corresponding estimates of gene frequency in the two populations. There are no satisfactory estimates of the frequency of this disease in the general population. Göthlin (1924) has very tentatively suggested an incidence of 1:300,000 in Sweden. The gene frequency figures, on the other hand, would suggest that the condition is somewhat more common.

5. Xeroderma pigmentosum. This rare disease is so striking that in the past a relatively high proportion of the cases seen in European medical centers have probably found their way into the literature. The condition appears to depend on a very specific alteration in metabolism which might have several different genetic bases but most probably has only one. The authoritative summary of Siemens and Kohn (1925) has been added to by Cockayne (1933) and by Macklin (1936). A total of 417 cases in 265 families had been reported up to 1933. Siemens and Kohn (1925) have pointed out that if all the reported cases are divided into those reported prior to 1906, and those recorded later, consanguinity is more common in the latter; this is probably a consequence of more thorough investigations in recent years. There is some evidence that the condition occurs more commonly in the offspring of marriages between Jews, and the consanguinity figures for this group may be different. Siemens and Kohn (1925) concluded that the true incidence of first cousin marriages in the parentage of the cases reported up to 1925 lay between 0.11 and 0.47. The first figure corresponds to the percentage of first cousin marriages in all the material, while the second corresponds to the incidence of first cousin marriages in the cases reported since 1906 for which there is a definite statement as to presence or absence of consanguinity. When allowance is made for the inclusion of Jewish cases, the true figure for the Gentiles in this material may not lie far from 0.25. Of the 43 cases summarized by Cockayne which have appeared since the paper by Siemens and Kohn, 10 may be discarded as occurring in Arabs, Jews, or Japanese. In the remaining 33, four were the offspring of first cousins, five of other consanguineous mating, for six there was no relationship, and for 18 there was no statement. The incidence of first cousin marriage in this group thus lies someplace between 0.12 and 0.27, with 0.20 being a not unreasonable figure. For purposes of calculation, then, we may assume that about 0.23 of the parents of individuals with xeroderma pigmentosum are first cousins.

The Japanese data are fairly extensive, and present the same problem as do the European. Komai (1947) presents only 13 sibships, five the outcome of consanguinity. However, Kawakami (unpublished) in a careful survey of the Japanese literature has found since 1894 reports of 382 cases in 252 sibships. Of these 252 sibships, 46 were the outcome of first cousin marriage, 10 were the outcome of consanguineous marriages of a degree stated to be other than first cousin, 25 were the result of consanguineous marriage the degree of

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

which was not stated, in 36 instances the parents were not consanguineous, and for 135 there was no statement. The true incidence of first cousin marriage in the parentage of this material thus lies between 0.18 and 0.61 (assuming in the latter figure that the 26 consanguineous marriages where the degree was not stated were all first cousins). An estimate of 0.40 for purposes of calculation would not seem to be unreasonable.

Table 5 shows that for the gene responsible for xeroderma pigmentosum, alone of the five studied, there appears to be a discrepancy between European and Japanese figures, with the gene more common in Japanese. This finding receives some support from the relative volume of Japanese publications on the subject, as well as the impressions of Japanese clinicians.

The rate of appearance of induced recessive mutations in European and Japanese populations

Haldane (1947) has touched upon the problem of the temporal distribution of recessive phenotypes due to mutations induced in a brief period during the life span of a single generation, as by an atomic bombing, in a population in which a certain degree of heterozygosity already exists. In his calculations he assumed an α value of 0.001, i.e., the value found by Orel plus "allowance" for consanguinity present but undetected. It is of interest to consider briefly the effect of a higher α value on this temporal distribution. If we deal with only a single genetic locus, represented in a population by two alleles, A, the (dominant) normal, and a, a (recessive) derivative, then in a panmictic population in genetic equilibrium, the following approximate relationship obtains:

$$m = (1-s)\left[\alpha q + (1-\alpha)q^2\right]$$

or, restated in terms of q,

$$q = \frac{-\alpha(1-s) + \sqrt{(1-s)^2\alpha^2 + 4m(1-\alpha)(1-s)}}{2(1-s)(1-\alpha)}$$

where α = the coefficient of inbreeding,
q = the frequency of the recessive allele under consideration,
m = the mutation rate from A to a per gene per generation - assumed at 1×10^{-5} - and
s = the selective value of individuals homozygous for the recessive allele under consideration (1.0 = normal) — here assumed at 0.5.

This is undoubtedly an oversimplification of any situation which might be encountered in nature, since, to mention only a few of the known complications, on the average each genetic locus is represented by more than two alleles, and reverse mutation from a $\longrightarrow$ A is not incorporated into the equation. The latter will usually be a negligible factor and can safely be neglected.

With these assumptions, equilibrium in a population where α = 0.00060 - the observed value for a European population - will be reached at q = 0.00418. Then α = 0.00372 - as in the Japanese population investigated - equilibrium will be reached at the lower q value of 0.00399. The frequency of the recessive phenotype will of course be the same in the two populations, namely, 0.00001.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

The tentative calculations of gene frequency in the preceding section have, however, failed to suggest the gene frequency differences demanded by the equilibrium formula. The explanation of this is in all probability to be sought in the fact that the relaxation of inbreeding characteristic of present day European populations is of so recent origin in terms of generations that it has not yet been reflected to an appreciable extent in gene frequencies (cf. Haldane, 1939). Therefore, in a consideration of the comparative genetic effects of an atomic bombing we may start with the fact that, so far as can be determined at present, the frequency of highly undesirable recessive genes is approximately the same in Japanese and European populations, being in both populations at a level fixed by a much higher incidence of consanguinity than obtains in present day European populations, with the corollary that because of a higher incidence of inbreeding the traits themselves are actually more common in the Japanese. This is not to infer, however, that the present Japanese population is in genetic equilibrium. It is probably more nearly so than European and American populations, but there are still many factors to disturb the genetic balance. Yet for the grossly unfavorable recessive genes, there has probably been a sufficient approach to equilibrium in the past (see below) to render permissible in a first approximation the use of the equilibrium formula to calculate the approximate frequency of recessive genes meeting certain requirements.

The effectiveness of irradiation in producing mutation in human genes is unknown. From analogy with the results in non-human material, we may assume, following the treatments of Haldane (1947) and Evans (1949), that the chance of mutation per gene per r in mature gametes is of the order of 2×10^{-8}. Then in a population of 100,000 survivors of an atomic bombing, each survivor having received on the average a dose of 100 r, the probability of an induced mutation at the locus under question in any gamete is $100 \times 2 \times 10^{-8}$, or 2×10^{-6}. This calculation involves the assumption that gonial cells, the source of gametes in the reproductive years following an atomic bombing, having the same sensitivity to irradiation as mature gametes, a point concerning which there are no exact data for mammals at the present time. Thus, in a population where q may be assumed originally to equal 0.003, the result of an atomic bombing as described above will be to increase q to 0.003002, i.e., the chance is 1 in 20 that in a population of 100,000 some one individual will have an induced mutation at the particular locus under discussion. The assumed contribution of 100 r to the total heterozygosity of the population is relatively small, and one-fifth that deriving each generation from the assumed spontaneous mutation rate for this locus. In connection with this statement, however, attention should be called to the unsatisfactory state of our knowledge concerning human spontaneous mutation rates; the figure of 1×10^{-5} per gene per generation used in this paper is the best approximation from a scanty data.

Haldane (1947) has pointed out that once the natural equilibrium which regulates gene frequencies has been disturbed by such an event as an atomic bombing, the return to equilibrium values will in a population where $\alpha = 0.0010$ require thousands of generations, with the rate at which recessive zygotes are to be expected rising in 200 years or less to a level somewhat in excess of $1/2\,\alpha$ if there is already considerable heterozygosity at the locus in question - which will usually be the case. Where the coefficient of inbreeding is six times higher, as in the present Japanese population, we may expect that the return to equilibrium will be accelerated, but the genetic effects of the bombing, being distributed over fewer generations, will be correspondingly more obvious.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Thus, following Haldane (1947), we may, disregarding selection and making assumptions as shown, calculate the "peak" genetic effect for an assumed particular locus in the two populations as follows:

Mean coeff. of Inbreeding	Initial Gene Frequency	Increased Gene Frequency	Initial Freq. of Recessives	Increment Recessives	"Equilibrium" Freq. of Recessives Before Selection
α	$\underline{q}$	$\underline{q} + \Delta \underline{q}$	$\alpha \underline{q} + (1-\alpha)\underline{q}^2$	$\Delta \underline{q}(\alpha + 2\underline{q})$	
.001	.003	.003 002	.000 011 991	.000 000 014	.000 012 005
.006	.003	.003 002	.000 026 946	.000 000 024	.000 026 970

As a result of this greater degree of inbreeding there will therefore be at the peak of the curve approximately twice as great an absolute effect when $\alpha = 0.006$, although the proportionate effect will actually be smaller. But in either case, the obvious impact on the population of induced mutation at this particular locus will be small indeed, amounting at the peak to about two individuals showing the trait per 100,000,000 persons. The total genetic impact of an atomic bomb on two such populations will be the summation of the genetic effects on thousands of loci, differing among themselves as to initial frequency of recessives, sensibility to irradiation, selective disadvantage of the homozygote, etc. If there were 50,000 loci each behaving as in the illustration above - a situation contrary to fact but useful for purposes of illustration - at the peak effect there would be 50,000 x 2/100,000,000, or on an average 1 per 10,000 persons showing the effects of an induced recessive mutation.

DISCUSSION

The observation that the coefficient of inbreeding is some six times as high in present day Japan as in comparable European populations immediately suggests the possibility of certain genetical consequences of this fact. However, attempts to utilize these data in various types of calculations rapidly leads to issues of some complexity. We realize fully the errors inherent in the relatively crude methods utilized here, and the sources of criticism. However, even if refined mathematical methods did exist, it is doubtful whether the data available for European and Japanese populations would justify their application. It is hoped that this communication has further emphasized a fact already recognized by many students of human genetics, namely, that the weaknesses which exist in the present day data concerning the genetics of human populations are no less extensive than the weaknesses in our mathematical tools for dealing with such data if they did exist. Valid studies of gene frequencies by indirect methods are as dependent upon an improvement in the quality of case reports and our knowledge of the breeding structure of human populations as on developments in mathematical theory. But when all due apologies have been made, the interesting fact remains that this first crude approach reveals in four out of five cases no apparent differences in gene frequencies in the two groups, although the ranges of error are very large. Despite these large errors, it appears

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

that the four genes whose frequencies have been found to agree in the two populations investigated may differ significantly among themselves as to incidence, i.e., in both populations the genes responsible for achromatopsia and albinism are almost certainly more common than those which produce ichthyosis congenita and infantile amaurotic idiocy. The frequency seriation thus established corresponds with the selective disadvantage which the various genes when homozygous confer upon their possessor. It is noteworthy that the calculated frequency of the genes responsible for albinism and congenital total color blindness - diseases where s approximates 0.5 - 0.6 is in satisfactory agreement with the values demanded by the equilibrium formula (p.) at an m level of 1×10^{-6}, as are the calculated values for infantile amaurotic idiocy and ichthyosis congenita, diseases where s is very close to 0.0. It is possible that the greater apparent frequency of xeroderma pigmentosum in Japanese is due to a higher s value in the latter group in consequence of skin pigmentation differences. Although man as a species is obviously not in genetic equilibrium, it seems probable that the biological unfitness of individuals with infantile amaurotic idiocy and ichthyosis congenita has not altered greatly in the past several thousand years, while the sociological and medical changes that currently permit individuals with congenital total color blindness and albinism to procreate as freely as individuals without these traits are of so recent origin as not yet to have affected gene frequency. That is to say, while the application of equilibrium formulae to the human species as a whole is certainly not permissible, for selected genes the situation may be such as to render it a valid procedure - as the present findings would seem to demonstrate.

It is a pleasure to acknowledge the aid we have received from Dr. C. W. Cotterman in the treatment of some of the statistical problems discussed herein.

CONCLUSIONS

1. The incidence of consanguineous marriage in Japan has been investigated in three Japanese cities, Hiroshima, Nagasaki, and Kure, and in two special areas, an Eta village (Midori Machi) and a fishing settlement (Daimu). Among women currently registering their pregnancies for ration purposes, the percent married to first cousins was 3.71 in Hiroshima (10,547 marriages), 4.10 in Kure (5,510 marriages), and 5.24 in Nagaski (7,747 marriages). A survey of all marriages in selected sectors of two of the cities revealed first cousin marriages in 3.93% of 3,283 Hiroshima unions, and 4.64% of 1,642 Kure unions. In the two special areas, first cousin marriages occurred in 5.44% of 147 Midori Machi unions and 7.12% of 323 Daimu unions. The coefficient of inbreeding in the two urban populations is 0.00372, some six times that of the only urban European population studied in this report.

2. Utilizing the theoretical relationship which exists under conditions of panmixia between gene frequency, consanguinity in the general population, and consanguinity in the parentage of individuals with various recessive diseases, very tentative calculations are made of the frequencies in European and Japanese populations of the recessive genes responsible for five diseases, namely, albinism, infantile amaurotic idiocy, achromatopsia, ichthyosis congenita, and xeroderma pigmentosum, assuming in each case a monogenic determination of the trait in question. It is emphasized that deviations from panmixia as well as deficiencies in the data very seriously limit the confidence which may be placed in the results of these calculations, so that the

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

results may be regarded only as a first approximation. It is found that the frequencies of four genes show a tolerable correspondence in the two groups, while one gene, xeroderma pigmentosum, may be more frequent in the Japanese.

3. Induced recessive mutations may be expected to manifest themselves significantly more rapidly in Japanese than in European populations if this difference in the coefficient of inbreeding persists.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

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Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

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Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

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Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Table 2.

Summary Table of Frequencies of Various Consanguineous Marriages in Different Kinds of Population in Kure and Hiroshima, Hiroshima Prefecture, Honshu, Japan

	Number of married couples	First cousin	First cousin once removed	Second cousin	Second cousin once removed	Third cousin	Third cousin once removed	Total number and percentage of all consanguineous marriages	In-law Marriages
Hiroshima (city)	3283	129 3.93%	38 1.16%	69 2.1%	18 0.55%	6 0.18%	1 0.03%	261 7.95%	76 2.39%
Kure (city)	1642	98 4.64%	31 1.47%	40 1.89%	5 0.24%	2 0.09%	0 0	176 8.33%	70 3.36%
Midori Machi (Eta village)	147	8 5.44%	3 2.72%	2 1.36%	0 0	1 0.61%	0 0	14 10.13%	10 1.47%
Dainu (village)	323	23 7.12%	6 1.86%	7 2.17%	1 0.31%	0 0	0 0	37 11.46%	9 2.79%
Total	5395	258 4.78%	78 1.45%	118 2.19%	24 0.44%	9 0.17%	1 0.02%	488 9.05%	115 2.13%

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Table 1. The frequency of consanguinous marriage among women registering as pregnant in three Japanese cities during 1948 and 1949.

City	Population (1947 Census)	Number of Women Registered	Number & Percentage of Various Types of Consanguinous Marriage: First Cousin	First Cousin Once Removed	Second Cousin	Other Consanguinity	Total Consanguinity
Hiroshima	224,100	10,547	391 (3.71%)	101 (.96%)	164 (1.56%)	28 (.27%)	684 (6.49%)
Kure	185,740	5,510	226 (4.10%)	79 (1.43%)	109 (1.98%)	17 (.31%)	431 (7.82%)
Nagasaki	198,642	7,747	406 (5.24%)	87 (1.12%)	153 (1.98%)	12 (.15%)	658 (8.49%)
		23,804	1,023 (4.30%)	267 (1.12%)	426 (1.79%)	57 (0.24%)	1,773 (7.45%)

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July - Dec. 1949

Table 3. The secular trend with respect to consanguinous marriages in the four areas studied.

a. As related to age of male partner

Degree of consanguinity	Male age group			
	21-40	41-60	61-80	Total
First cousin	94 (4.24%)	87 (4.08%)	26 (4.73%)	207 (4.23%)
First cousin once removed	36 (1.62%)	21 (0.99%)	6 (1.09%)	63 (1.29%)
Second cousin	65 (2.93%)	31 (1.45%)	11 (2.00%)	107 (2.18%)
Total marriages	2217	2131	550	4898

b. As related to age of female partner

Degree of consanguinity	Female age group			
	17-40	41-60	61-80	Total
First cousin	122 (4.07%)	68 (5.03%)	18 (5.90%)	208 (4.47%)
First cousin once removed	42 (1.40%)	25 (1.85%)	1 (0.33%)	68 (1.46%)
Second cousin	76 (2.53%)	20 (1.48%)	7 (2.30%)	103 (2.21%)
Total marriages	2999	1353	305	4657

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Table 4.
Summary Table of the Frequency of Various Degrees of Consanguineous Marriage in Different Types of Population Units in Kumamoto Prefecture, Kyushu, Japan.

	I	II		III		IV		V		VI		VII		VIII	
	Number of Married Couples	First cousin		First cousin once removed		Second cousin		Second cousin once removed		Other consanguineous marriages		Seem to be consanguineous but uncertain		Total (excluding VII)	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Kumamoto City (city)	1830	63	3.4	31	1.6	23	1.2	6	0.3	0	0	6	0.3	124	6.7
Yamashika (town)	2902	162	5.5	42	1.4	46	1.5	19	0.6	3	0.1	4	0.1	276	9.5
Waifu (town)	2908	175	6.02	48	1.6	52	1.7	16	0.5	3	0.1	12	0.4	298	10.2
Udo (town)	1092	56	5.1	15	1.0	26	2.3	3	0.2	2	0.1	4	0.3	103	9.4
Toride (village)	459	39	8.5	13	2.8	12	2.6	1	0.2	2	0.4	0	0	68	14.8
Hanabusa (village)	390	33	8.5	6	1.5	10	2.5	3	0.7	0	0	0	0	52	13.3
Kikuchi (village)	888	84	9.4	14	1.5	26	2.9	11	1.2	0	0	4	0.4	142	15.9
Asahino (village)	416	28	6.7	15	3.6	12	2.8	3	0.7	1	0.2	3	0.7	59	14.1
Suigen (village)	776	96	12.4	29	3.7	15	1.9	11	1.4	1	0.1	2	0.2	152	19.5
Higashi Nagashima (village)	1788	204	11.4	45	2.5	57	3.1	26	1.4	1	0.05	24	1.3	336	18.7
Nishi Nagashima (village)	1433	205	14.3	38	2.6	55	3.8	18	1.2	2	0.1	13	0.9	320	22.3

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File:

Table 5.
The incidence of consanguinity in various types of European population groups. For purpose of convenience, the material has somewhat arbitrarily been classified into "normal populations" and "isolates".

a. Normal populations

Author	Material	Period	Frequency of first cousin marriages	Frequency of consanguinous marriages up to and including second cousins.
Lenz, 1919	World literature plus assumptions as to number of consanguinous marriages not so stated, with reference to European populations.	±1875-1910	1.0%	2.6%
Spindler, 1922	453 Catholic and Protestant marriages in 3 villages in rural Würtenberg, Germany	±1875-1920	1.8 ± 0.7%	9.6 ± 1.4%
Wulz, 1925	5,283 marriages in 40 Bavarian parishes - predominatly a rural Catholic population	1848-1872	0.49 ± 0.096	1.07 ± 0.14
	5,706 marriages in 40 Bavarian parishes - predominantly a rural Catholic population	1873-1897	0.65 ± 0.11	1.33 ± 0.15
	5,193 marriages in 40 Bavarian parishes - predominantly a rural Catholic population	1898-1922	0.67 ± 0.11	1.52 ± 0.17
Orel, 1932	40,697 Catholic marriages in Vienna and environs	1901-1902	0.77 ± 0.043	1.12 ± 0.052
	44,911 Catholic marriages in Vienna and environs	1913-1914	0.68 ± 0.039	1.24 ± 0.052
	31,823 Catholic marriages in Vienna and environs	1929-1930	0.53 ± 0.041	0.99 ± 0.056

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

TABLE 5. (CONT.)

b. "Isolates"

Author	Material	Period	Frequency of first cousin marriages	Frequency of consanguinous marriages up to and including second cousins
Pearson, 1911	448 marriages in 12 Fijii Island villages where local custom encouraged c[illegible] cousin marriages	±1850-1895	29.7 ± 2.2	
Reutlinger, 1922	117 marriages among Hohenzollern Jews	±1875-1920	16.2 ± 3.4%	19.6 ± 3.7%
Brenk, 1931	270 marriages in an Alpine community in Switzerland	±1870-1923	1.9 ± 0.8%	9.7 ± 1.8%
auf der Nöllenberg 1932	380 marriages in an isolated Protestant community of Rhineland, Germany	1840-1889	5.3 ± 1.2%	11.1 ± 1.6%
Egenter, 1934	52 marriages in Obermatt, Switzerland	±1890-1932	11.5 ± 4.4%	53.8 ± 6.9%
Grob, 1934	139 marriages in an Alpine community in Switzerland	±1885-1932	0.7 ± 0.7%	9.9 ± 2.5%
Ruepp, 1935	77 marriages in an Alpine community in Switzerland	±1880-1933	3.9 ± 2.2%	19.5 ± 4.5%
Sjögren, 1948	Parents of 332 randomly selected persons on a small, rural Swedish Island	±1850-1920	3.0 ± 0.9%	
Böök, 1948	All marriages in the populations of three Northern Swedish parishes:	±1880-1945		
	Pajola (population of 5943)		1.0 ± 0.3	
	Junosuando (population of 1871)		2.9 ± 1.0	
	Muonionalusta (population of 1376)		6.8 ± 1.8	

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Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949

Table 5. (cont.)

Author	Material	Period	Frequency of first cousin marriages	Frequency of consanguinous marriages up to and including second cousins
Dahlberg, 1939	1,286,339 marriages contracted in Prussia	1875-1880	0.71 ± 0.0074	
	2,122,300 " " " "	1921-1926	0.20 ± 0.0033	
	188,973 " " " Bavaria	1876-1880	0.87 ± 0.021	
	474,268 " " " "	1926-1933	0.20 ± 0.0066	
	1,410,889 " " " France	1876-1880	1.03 ± 0.0085	
	1,350,683 " " " "	1914-1919	0.97 ± 0.0085	
Bell, 1940	Parents of 49,315 adult in-patients of general hospitals in England	±1880-1925	0.61 ± 0.035	*
	Parents of 10,236 child in-patients of general hospitals in England	±1925-1939	0.40 ± 0.062	
Bartels, 1941	Parents of 498 randomly selected young propositi in Copenhagen, Denmark	±1900-1920	1.2 ± 0.5%	

* Because of the manner of selection of this material, these figures are undoubtedly higher than those for the population at large.

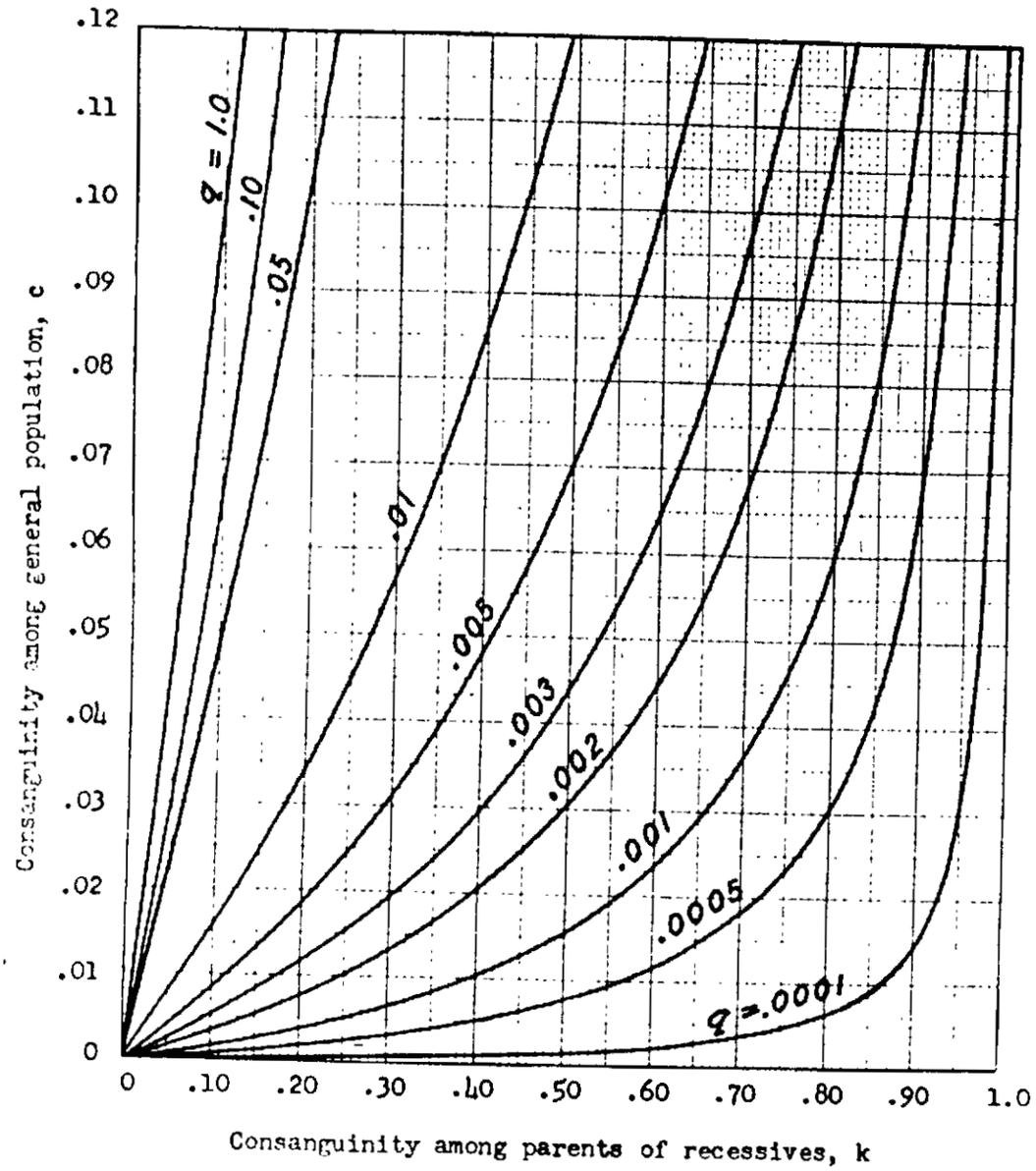
Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July - Dec. 1949

Table 6.

The incidence of consanguinity in the parentage of individuals with certain recessively-inherited diseases, and the gene frequencies which may be calculated therefrom. Further explanation in text.

Trait	Caucasian (predominantly European)			Japanese		
	Incidence of first cousin marriages in parents (k)	Authority	q	Incidence of first cousin marriages in parents (k)	Authority	q
1. albinism	0.18 - 0.24	Pearson, 1913	0.0021-0.0030	0.37 - 0.59	Kurasima, 1937	0.0029-0.0075
2. infantile amaurotic idiocy	0.27 - 0.53	Slome, 1933	0.0006-0.0018	0.55 - 0.85	Katsunuma, Murakami, and Takesita, unpublished	0.0007-0.0034
3. ichthyosis congenita	0.30 - 0.40	Cockayne, 1933	0.0010-0.0015	0.67 - 0.93	Yamamoto and Ishikawa, 1939	0.0003-0.0022
4. congenital total color blindness	0.11 - 0.21	Peter, 1926; Bell, 1933; Göthlin, 1941	0.0025-0.0055	0.39 - 0.51	Hohki, Hitomi, 1943	0.0041-0.0069
5. xeroderma pigmentosum	0.20 - 0.26	Siemens and Kohn, 1925; Cockayne, 1933 Macklin, 1936	0.0019-0.0026	0.37 - 0.43	Kawakami, unpublished	0.0057-0.0075

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July-Dec. 1949



Recessive gene frequency (q) as a function of the frequency of first cousin mating among the general population (c) and among the parents of recessives.(k).

$$q = \frac{c(1-k)}{16k - 15c - ck}$$

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 54A-0064
Box #: 4
File: 040 (National Research Council) July - Dec. 1949