Empirical Risks in Consanguineous Marriages: Birth Weight, Gestation Time, and Measurements of Infants[1]

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EXTENSIVE OBSERVATIONS on plants and animals support the generalization that increased morbidity and decreased size and vigor are the immediate effects of inbreeding on a normally outbred population. Genetic experiment and theory agree in attributing these results to the manifestation in a homozygous state of genes ordinarily heterozygous. An accumulated load of deleterious recessive mutations is inevitable in a cross-fertilizing species, and most inbreeding effects seem to be consequent on this. Other evidence indicates that selection sometimes favors the heterozygote over either homozygote, but the importance of such overdominance is poorly understood. For both mechanisms change in homozygosis is an appropriate measure of the inbreeding effect (East and Jones, 1919; Wright, 1921; Crow, 1952).

In man, cases of rare recessive diseases are often the issue of consanguineous marriage, and conversely, the frequent occurrence of parental consanguinity may be considered indirect evidence of a recessive component in diseases whose inheritance is uncertain. A comprehensive and reasonably restrictive estimate of inbreeding effects requires a large body of data and a relatively high incidence of consanguineous mating. Such material has recently become available through the genetics program of the Atomic Bomb Casualty Commission in Japan (Neel and Schull, 1956).

COLLECTION OF THE DATA

The data of this study have been collected as follows (Schull, 1958). During the years 1948–1954 in Hiroshima and Nagasaki, and 1948–1950 in Kure, a registration system for pregnant mothers was maintained in conjunction with the city offices responsible for the carrying out of rationing laws. Under this system, registrants reporting for special ration cards at about the fifth month of pregnancy were interviewed by Commission clerks, who obtained data on age, consanguinity, previous pregnancies, date of the last menstrual period, exposure to the atomic bombs, and other matters. At the time of birth of a child so registered, the cooperating midwife or physician reported on the onset and course of labor, sex, type of termination, and birth weight. Birth weight was determined after July, 1949, on scales distributed by the Commission, but before then on the attendants' own scales. Commission clerks computed gestation time from the registration record of the last menstrual period, if this had been ascertained. In an unknown fraction of the cases the date of

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the last menstrual period was not known, but was taken from the attendants' records, or from the mother after the child was born, or rarely, estimated from the appearance of the baby. A Japanese physician in the employ of the Commission examined each baby, promptly if it was reported by the attendant to be abnormal, and usually within 2 or 3 weeks if the termination was reported normal. Consanguinity information obtained by the registration clerks was verified at this home visit. For all "abnormal" cases (as defined, these included nearly 20 per cent of all cases) and for a 10 per cent sample (those registration numbers ending in zero) a more detailed report was made, including the results of a test for maternal syphilis, gynecological history, a rating of economic status, and autopsy data, if any. In addition, a sample of infants surviving to the age of about 9 months was selected by the terminal registration number and examined in the clinic. For the study of infant measurements, age at examination has been restricted to 8, 9, and 10 months.

RELIABILITY OF THE CONSANGUINITY DATA

Evidence has been presented elsewhere that errors in determining degree of inbreeding may probably be neglected (Schull, 1958). There is reason to believe that techniques of measurement were unbiased with respect to consanguinity. Moreover, estimates of consanguinity effects from different cities and from midwives' and clinical data are in good agreement for all anthropometrics, and there is no indication of measurement bias with regard to exposure history which from the nature of the investigation was most subject to bias (Neel and Schull, 1956).

This does not imply, of course, that estimates of inbreeding effects from these data will necessarily be free from the extraneous effects of sociological concomitants of consanguineous marriage. Schull (1958) has reported that in this population consanguineous marriages were significantly associated with urban origin, non-exposure to the atomic bomb, a low incidence of induced abortions, a high number of conceptions, and low maternal age. Over the period of observation there has been a significant decrease in the reported incidence of consanguineous marriage. There was no association with birth injury or economic status as measured.

Even if consanguineous marriages do not differ from unrelated ones in unmeasured factors, the isolation of genetic effects from this tangle of sociological differences is uncertain. There is no indication of an association between radiation history and any of these anthropometrics (Neel and Schull, 1956). The effects of induced abortion have been eliminated as well as possible by excluding all known induced terminations. Stillbirths, neonatal deaths, and major congenital malformations have likewise been excluded. In addition to estimating the relation between inbreeding and defect from the pooled data, the material has been partitioned in different analyses by city, parity, radiation history, sex, age in months, and year of birth, and data from mothers negative for the syphilis test have been analysed separately for birth weight. None of these more detailed analyses gave estimates which differed appreciably from those obtained from the pooled data, and estimates of inbreeding effects from different degrees of consanguinity, omitting unrelated parents, agree with independent estimates from children of related and unrelated parents (table 2). Since any sociological concomitant of inbreeding might be expected to differ more between children of related and unrelated parents than among different degrees of relationship, these observations suggest that, in this material, the estimates of genetic effects are not biased by extraneous factors.

ANALYSIS AND RESULTS

Schull (1958) gives the reported incidence of consanguineous parentage among the registrations for 1948–1954. Second cousins, first cousins once removed ($1\frac{1}{2}$ cousins), and first cousins account for nearly all cases ascertained, the remainder being largely composed of remote or unspecified relationships. In this material, ascertainment of consanguinity more remote than second cousins was not reliable, and only parents recorded as first cousins, $1\frac{1}{2}$ cousins, second cousins, or unrelated have been used to estimate empirical risks. Parents are termed unrelated if they are not known to be related. Unless marriages of more remote relatives take place considerably more frequently than they would with random mating, and very much more frequently than our records indicate, the inbreeding coefficients of the four groups may be taken to be $\frac{1}{16}$, $\frac{1}{32}$, $\frac{1}{64}$, and 0, respectively (Wright, 1921).

The inbreeding coefficient (F) was defined by Wright so as to be proportional to reduction in heterozygosity. Insofar as selection and epistasis may be neglected, it is obvious from this definition that the inbreeding effect on the mean of a quantitative character is proportional to F:

$$m_F = m_0 - (m_0 - m_1)F$$

where m is the mean, $m_0 - m_1$ is estimated as a regression coefficient, and the subscripts 0, 1, and F denote no inbreeding, complete inbreeding and intermediate inbreeding, respectively (Wright, 1951). This approximation should give good results over small ranges of F, but for larger intervals deviations from linearity may become apparent, due to the damping or accelerating effects of selection and epistasis. As a test of linearity, the regressions for the three degrees of non-zero inbreeding (b_{FF}) and for inbred children vs. outbred children (b_{FO}) have been calculated in addition to the mean $\bar{b}$. Over the observed range of inbreeding from 0 to $\frac{1}{16}$, the two independent estimates agree closely for all the measurements of the present study (table 2), but there is little basis for estimating how important deviations from linearity might be if higher values of F could be observed.

Prima-facie evidence for inbreeding effects is given in table 1 as the pooled numbers of observations and means for the six measurements. For birth weight there is a slight decrease with inbreeding, and with more than 70,000 observations this is significant even when the unrelated group is excluded. Length of gestation, with almost the same number of observations, shows no effect of inbreeding. The gestation time of normal infants may well be determined by maternal characteristics, in which case it would not be expected to respond to inbreeding of the fetus. Inbreeding decline in the measurements of 8, 9, and 10 months infants is highly significant for weight and height. These conclusions are reinforced by the more detailed analysis within parity, city, age, and sex, by which analysis the effect of inbreeding on chest girth is also highly significant (table 2). Estimates from the three cities are homogeneous. There is no significant effect of inbreeding on the variances of individuals

Table 1. Pooled data on infant measurements and relationship of parents

	Unrelated	second cousins	1½ cousins	first cousins
		Means		
Weight of live births (dkg.)	307.4	307.1	307.1	304.6
Length of gestation (wks.)	40.13	40.22	40.11	40.13
Weight at 8–10 months (dkg.)	781.8	778.5	776.5	772.2
Height at 8–10 months (mm.)	689.6	689.3	689.8	687.3
Head girth at 8–10 months (mm.)	442.8	444.0	442.5	442.8
Chest girth at 8–10 months (mm.)	427.7	427.6	428.3	426.8
		Number of Observations		
Birth weight	70088	1252	892	2928
Gestation	58605	1058	766	2517
Metrics at 8–10 months	18501	330	244	815
		Inbreeding Coefficient		
	0	1/64	1/32	1/16

Table 2. Regression coefficients of infant measurements on inbreeding (F) and their standard errors

	Pooled data $\bar{b}$	Within groups* b_{FO}	Within groups* b_{FF}	Within groups* $\bar{b}$
Weight of live births (dkg.)	−42 ± 12	−55 ± 13	−51 ± 29	−54 ± 12
Length of gestation (wks.)	.01 ± .70	.24 ± .78	−1.6 ± 1.7	−.10 ± .70
Weight at 8–10 months (dkg.)	−156 ± 50	−121 ± 53	−114 ± 117	−120 ± 48
Height at 8–10 months (mm.)	−34 ± 14	−24 ± 14	−46 ± 31	−28 ± 13
Head girth at 8–10 months (mm.)	1 ± 8	−7 ± 8	−25 ± 17	−10 ± 7
Chest girth at 8–10 months (mm.)	−12 ± 11	−28 ± 11	−33 ± 25	−29 ± 10

* The groups are city × parity × year for birth weight, city × parity for length of gestation, and city × sex × age in months for other measurements.

Table 3. Regression of the within-group variance of individuals on F, with the standard error of the regression coefficient

	$\sigma^2 + bF$	s_b
Weight of live births (dkg.)	1750 − 177 F	736
Length of gestation (wks.)	5.0 − 1.0 F	2.3
Weight at 8–10 months (dkg.)	7500 + 9035 F	6337
Height at 8–10 months (mm.)	538 + 504 F	445
Head girth at 8–10 months (mm.)	158 + 153 F	132
Chest girth at 8–10 months (mm.)	351 + 464 F	297

(table 3), although these tend to increase with inbreeding as expected. A much larger series of observations would be required to estimate the genetic variance from the regression of the phenotypic variance on inbreeding (as sugsgeted by Hogben, 1933). The data are fully consistent with the hypothesis that in breeding causes a decline in infant measurements, but the magnitude of this decline is extremely small and can be detected only in very large samples.

DISCUSSION

Some of the consequences of inbreeding in man may be deduced from the present estimates of genetic effects, assuming that these are unbiased. With regard to first-cousin marriages (F = .0625), the effect of inbreeding is estimated from $\bar{b}$ within groups (table 2) to be a decline of about 3.4 dkg. for birth weight, 7.5 dkg. for weight at 8–10 months, 1.8 mm. for height at 8–10 months, 1.8 mm. for chest girth at 8–10 months, and 0.6 mm. for head girth at 8–10 months. Such small decreases in body size must in themselves have only a slight, but perhaps not negligible, effect on infant survival. As for the effect of consanguineous marriages on infant size in the population, this is insignificant even in Japan, where consanguineous marriages are relatively common (Neel *et al.*, 1949). In our data, for example, the average inbreeding coefficient is .0031, or about 5 per cent as great as the inbreeding coefficient of first cousins, so that complete elimination of consanguineous marriages would have an effect on the population only 5 per cent as great as the effect of first-cousin parentage; decreasing the frequency of consanguineous marriage by a smaller amount, as Roman Catholicism has done for its adherents in Japan, would have a proportionately smaller effect (Schull, 1953).

Close consanguineous mating in human populations may be a less important form of inbreeding than isolation by distance or other barriers (Dahlberg, 1948). The magnitude of this inbreeding is difficult to assess, although Wright (1950) has suggested that it is not likely to be greater than F = .02, which corresponds to an isolate size of about 200 families. Accepting .02 as the maximum reduction in inbreeding brought about by increased dispersion in recent generations, it appears from table 2 that this "isolate-breaking" cannot account for an increase of much more than 1 dkg. in birth weight, 2 dkg. in weight at 8–10 months, and fractions of a millimeter in height, head girth, and chest girth at 8–10 months. Temporal changes in infant body size of greater magnitude than this must therefore be largely due to changes in nutrition or other environmental factors. Takahashi and Oshio (1938), comparing babies born at the Red Cross Hospital, Tokyo, in 1926–27 and again in 1937–38, observed an increase in birth weight of 7.4 ± 0.8 dkg., and in our own data for the postwar period 1949–1954, the increase in birth weight of children of unrelated parents, within parity and city, was 0.69 ± 0.12 dkg. per year. Ikuchi and Okuda (1927) compared Osaka babies examined in 1924–25 with Japanese standards published in 1902, and if the two groups are really comparable, it would appear that for babies at the age of 8–10 months, there had been an increase of several millimeters in height, head girth, and chest girth, and of more than 20 dkg. in weight, which is far too great to be attributed to isolate-breaking. This conclusion of course cannot be extrapolated to temporal changes in adult measurements, and inbreeding may have a greater effect on adult characteristics, as Dahlberg (1948) has suggested. However, there is no evidence that this is the case, and data on other mammals suggest no great increase of inbreeding effects with age, except perhaps for weight, which at birth is considerably influenced by maternal factors (Morton, 1955; Tyler, Chapman and Dickerson, 1949; Dickerson et al., 1954). It may be doubted, therefore, whether any appreciable fraction of the increase in size observed during recent generations in

Japanese and Western populations can be attributed to increase in heterozygosity through isolate-breaking.

SUMMARY

Offspring of unrelated parents, first cousins, first cousins once removed, and second cousins have been examined in three Japanese cities. The reliability and validity of the data are discussed. Taking account of city, parity, sex, and other relevant variables, the effects of inbreeding are estimated for birth weight, gestation time, and measurements of infants at the age of 8–10 months. For length of gestation and head girth no significant effect is detected. There is a small but significant decrease in weight, height, and chest girth with inbreeding. However, even for first-cousin matings the decrease in body size is slight. There is no significant effect of inbreeding on the variances of these measurements. The effects of "isolate-breaking" and of the prohibition of cousin marriage on body size are discussed, and it is concluded that these effects are likely to be quite small.

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