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The Effects of Parental Consanguinity and Inbreeding in Hirado, Japan. V. Summary and Interpretation

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INTRODUCTION

In a series of recent papers we have described the results of a study on Hirado Island, Japan, primarily directed toward the effects of parental inbreeding on reproductive performance and offspring characteristics, but also supplying extensive data on consanguinity effects [1–4]. The paucity of data on parental inbreeding effects has until now seriously hampered efforts to utilize the results of the marriage of related individuals to understand the genetic structure of human populations. It will be the purpose of this final paper to summarize and integrate the findings of the preceding papers as well as the results of previous studies by ourselves and others in Japan, and to utilize these findings to explore such questions as the role of reproductive compensation in the rate of elimination of deleterious recessive genes, the extent to which the genetic polymorphisms are maintained by active selection, and the complementarity of the results of studies on outbreeding with those on inbreeding. The term "consanguinity effects" will, in the usual fashion, refer to the effects of consanguinity of the parents on offspring characteristics, whereas "inbreeding effects" refer to the effects on offspring characteristics of one or the other of the parents being the product of a consanguineous marriage.

A. A SUMMARY OF THE RESULTS OF CONSANGUINITY AND PARENTAL INBREEDING ON HIRADO

Before proceeding to a consideration of inbreeding and consanguinity effects, we must briefly consider the pervasive problem of differences in socioeconomic status (SES) between consanguinity classes.

1. *The Pervasiveness and Variable Nature of Socioeconomic Biases*

Consanguineous marriages are generally less frequent than nonconsanguineous ones in most countries and locales. Commonly they constitute less than 10% of all marriages; their infrequency raises, of course, questions as to how representative of the general population these individuals are. Most studies of consanguinity and inbreeding effects have ignored possible socioeconomic biases; however, among

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those which have examined this issue, with but a few exceptions all have found significant socioeconomic differences among consanguinity classes. Where differences have not been observed, the series was often small. For instance, Krieger [5, 6] reports no differences in a study with fewer than 300 children with coefficients of inbreeding as great as or greater than first cousins (representing at most 60-odd families); important socioeconomic differences of the magnitude to be reported shortly could readily pass undetected under these circumstances.

Insofar as Japan is concerned, we have reported earlier that in Hiroshima and Nagasaki socioeconomic status, as measured by a socioeconomic score based upon occupation, education, household density, and expenditures on food, decreases significantly and systematically with parental relationship [7]. Failure to adjust for this bias would have resulted in an overestimation of the importance of consanguinity effects in virtually every one of some 25 measures of physical and mental growth and development; overestimation would have ranged from a few to as much as 20% of the estimate itself. The pervasiveness of the socioeconomic bias in this instance prompted careful exploration of possible socioeconomic differences in the study on Hirado. Again, significant differences emerge, but of a somewhat more complex nature.

Subdivision of Hirado's families into farm and nonfarm groups corresponds roughly to a rural-urban subdivision. Within the nonfarm group the frequency of consanguineous marriages increases as socioeconomic status decreases, and in a manner consonant with the changes seen in Hiroshima and Nagasaki, particularly the latter. Among farming families, however, the opposite obtains, that is, the frequency of consanguineous marriages is positively correlated with economic status. Cultural reasons can be adduced to account for these differences. The existence of biases of this nature could not in our estimation be ignored, and their effects have been routinely estimated and removed. Parenthetically, it deserves noting that even if socioeconomic factors were uniformly distributed over consanguinity classes, their removal would be warranted to reduce the error variances, and hence to improve the sensitivity of the tests of significance.

Morton [8], reviewing our earlier study in Hiroshima-Nagasaki [7], has written: "With so little environmental comparability among consanguinity groups, the reader is left to wonder how the estimates and their significance would be altered if all the confounding environmental variation could be eliminated." Likewise, we read in Krieger [5], ". . . the results of Schull and Neel and my results should be weighted differently, since, although the present sample may be heterogeneous with regard to background noise, the heterogeneity of the Japanese material is a fact, thus biasing to an unknown extent the inbreeding effects. . . ." It is probably the inevitable price of recognizing clearly the extent to which experiments of nature may be confounded by extraneous variables to be subjected to this type of criticism. The comments chose to disregard the extensive fashion in which the analysis adjusted for the extraneous variables. That these factors continue to operate in migrant groups is shown clearly by the data of Freire-Maia et al. [9] on Japanese immigrants to Brazil. In fact, the apparent SES differences between consanguineous

and nonconsanguineous marriages of Japanese Brazilians are at face value greater than encountered in Hiroshima and Nagasaki by ourselves, and suggest a revision downward of the low B/A ratio reported by Freire-Maia et al. If socioeconomic differences between classes of consanguineous marriages of a degree capable of modifying the indicator traits can be demonstrated on an island such as Hirado, then surely no locale can be beyond suspicion in this respect.

No future study which fails to take this possible bias into account meets contemporary standards. The use of sibling controls does not preclude consideration of socioeconomic factors—we submit that the individual who marries his cousin will be found to differ in many ways from his sibling who does not. Support for this viewpoint is to be found in the recent paper of Freire-Maia and Azevedo [10] where, incidentally, the apparent loss of significant extraneous differences between consanguineous and control material as one moves from "random" controls to "sibling" controls is due as much to a reduction of numbers as to any change in absolute values (cf. their tables 1 and 2). Among the six significant differences between the consanguineous material and the "random" controls not demonstrable when "sibling" controls are used, in two instances the absolute differences are greater in the latter comparison, and in the remaining four the smaller difference stems more from a shift in the mean of the consanguineous material than from a change in the mean of the control. The burden of proof is now on the investigator who states that in his study socioeconomic differentials between consanguinity classes did not exist. To the extent possible, *the findings to be summarized below have been adjusted for SES differences between classes of subjects.*

2. *Consanguinity Effects on Hirado*

These will be summarized under three headings:

a) Effects on mortality. Pregnancy-by-pregnancy enumerations from which the effects of consanguinity on mortality could be appraised were available for the reproductive performances of some 10,530 marriages represented by one or more spouses alive and residing on Hirado in the summer of 1964. Of these marriages, 15.7% were consanguineous, and in an additional 16.3% one or the other or both parents could be shown to be the product of a consanguineous marriage. These enumerations specified the nature of each pregnancy termination, that is, fetal death, stillbirth, or live birth; and if the latter, whether the individual was alive or dead at the time of enumeration. Within these data, there was no significant effect of consanguinity upon the frequency of stillborn infants; however, the frequency of nonaccidental deaths of liveborn infants prior to their twenty-first birthday increased significantly with parental relationship. Cumulative mortality was elevated by approximately 0.75% per percent fetal inbreeding (actually, 0.77 ± 0.16).

b) Effects of physical and mental characteristics. Middle School children and their parents served as the subjects for this portion of the study. These children resided in areas of the island known to have levels of consanguineous marriages and parental inbreeding somewhat above the average. Of the 1,555 children, 21.4%

resulted from known consanguineous marriage; of the 1,759 parents, the corresponding figure was 13.8%. The physical and mental characteristics employed as possible indicators of consanguinity effects were, for both children and adults: (1) physical development, (2) systolic and diastolic blood pressure, (3) tapping rate, (4) notable disease of the eye and ear, (5) visual accommodation, (6) visual acuity, (7) auditory acuity, and for the children only, (8) IQ and (9) school performance. The only significant consanguinity depression is on tapping rate in adults. However, taken at face value, the depressing effects of consanguinity on (1), (3), (8), and (9) are very similar to those encountered in a study on consanguinity effects in Hiroshima and Nagasaki children [7]; failure to achieve significance in the present study probably reflects the smaller numbers. But in contrast to the Hiroshima-Nagasaki study, there is in the present results no suggestion of a consanguinity effect on (4), (5), (6), and (7). Trait 2 (blood pressure) shows no consanguinity effect in either study, so that we are unable to confirm Krieger's [5] report of a significant effect of consanguinity on diastolic blood pressure in a Brazilian population.

c) Effects on fertility. Total pregnancies and total live births were significantly increased with consanguinity, but "net fertility," defined as total live births minus nonaccidental deaths prior to age 21, was not when allowance was made for the role of socioeconomic factors and religious affiliation was ignored. Significantly more "childless" marriages, those stated by husband, wife, or both to have produced no issue, occur among the nonconsanguineously married than among the consanguineous. On the basis of the Hirado data, a first-cousin marriage has approximately one chance in 20 of being without children whereas there is one chance in 10 that unrelated spouses will be childless. The frequencies of these marriages alone does not account for the fertility differences just described.

Among Buddhists, the only religious group large enough to warrant separate analysis, total pregnancies, total live births, and "net fertility" were all significantly and positively associated with parental relationship. However, the regression coefficient associated with "net fertility" is less than half the value associated with either total pregnancies or total live births in this instance. There is thus some evidence for reproductive compensation in association with the excess mortality due to inbreeding of the fetus, sufficient to lead us to explore in a subsequent section what such compensation might imply in formulations relating loss of deleterious recessive genes to inbreeding. (In this context, reproductive compensation generally implies the replacement of children who die young.)

3. *Inbreeding Effects on Hirado*

These will be summarized under the same three headings:

a) Effects on mortality. No consistent effect of paternal inbreeding on the frequency of stillborn infants nor upon the frequency of prereproductive mortality among liveborn children emerged. Maternal inbreeding did appear to have an effect, albeit an equivocal one, on the frequency of prereproductive mortality; the latter increased with increasing inbreeding, at a rate at most of 0.5% per percent

of inbreeding. The increase appears to be restricted to the first year of life expectation.

b) Effects on physical and mental characteristics. The search for effects of paternal and maternal inbreeding was in the adults restricted to traits (1), (2), and (3), as listed earlier, because of the more favorable analytic opportunities for continuously distributed variables when the numbers are as small as for the adults in this series. However, for the children, the examinations extended to all nine traits. Among the children, 13.1% of their fathers and 11.6% of their mothers were known to be inbred. With respect to the parents of the children, 2.2% of their fathers and 3.1% of their mothers could be shown to be inbred, the lower percentages reflecting the difficulty in establishing the consanguinity of a marriage occurring about 1900. No significant effects or suggestive patterns were observed. A standard criticism of efforts to utilize consanguinity and inbreeding effects (especially mortality) derived for civilized groups to explore the genetic structure of human populations is that to appreciate genetic loads one really needs data gathered under the harsher conditions to which primitive man was subject. The present data provide no evidence that being the offspring of an inbred parent marks a child in such a way that under harsher conditions his survival after the neonatal period might be impaired.

c) Effects of fertility. Among nonfarm marriages, all three measures of reproductivity—total pregnancies, total live births, and "net fertility"—were increased significantly with paternal inbreeding, irrespective of whether religious affiliation was ignored or restricted to Buddhists. Among farm marriages, these measures were decreased but not significantly so. The differences between farm and nonfarm communities are significant. No simple explanation other than chance can be advanced for this finding; however, it is possible that this is but another manifestation of the differences in motivation underlying consanguineous marriages in farm and nonfarm groups to which allusion has been made. Total pregnancies and total live births, but not "net fertility," increase significantly with maternal inbreeding among nonfarm marriages; within farm marriages, these three metrics also increase, but significantly so only in the case of total live births.

B. A COMPARISON OF THESE RESULTS WITH THOSE OF OTHER STUDIES IN JAPAN

How representative are the Hirado findings? Schull and Neel [7] have reviewed the results through mid-1963 of the principal studies on the effects of consanguinity on mortality in Negroes, Indians, Orientals, and Caucasians, concluding that "there is no convincing evidence that the effects of inbreeding on mortality differ in these racial groups." At that time the possibility of significant differences in inbreeding effects between Negroes and Caucasians in Brazil was strongly supported by Freire-Maia and collaborators. These investigators have now retreated from that position [10, 11]. In our earlier review, there appeared a greater similarity in the results of the various studies on Japanese than on Caucasian and Indian groups. The several studies on Caucasoid populations since then have confirmed this impression [12–20]. In our view this greater similarity of the Japanese results can

best be interpreted as indicating that despite the recognized socioeconomic differences between consanguineous and nonconsanguineous marriages in Japan, these differences are probably less confounding in Japanese than in other major ethnic groups. At any rate, we shall leave to those who work with Caucasian and Negro populations the problems of reconciling this greater variability and in this section derive a composite picture only for the studies on Japanese.

The effects in Japan of consanguinity on the combined frequency of stillbirths and deaths through a variable period of childhood are summarized in table 1, utiliz-

TABLE 1

RESULTS OF VARIOUS STUDIES ON EFFECT OF INBREEDING ON DEATH DURING INFANCY, CHILDHOOD, AND YOUNG ADULTHOOD AMONG JAPANESE

Investigator and Locale	*A*	*B*	*B/A*	Data Base	Size of Inbred Sample	Ascertainment
Watanabe [22]:						
Fukushima Prefecture	0.0881	0.5157	5.8	LB	4,594	Through child surviving to high school
Tanaka [23], Kishimoto [24]:						
Shizuoka	0.1253	0.7191	5.7	LB	2,205	Through child surviving to elementary school
Schull et al. [25]:						
Nagasaki Prefecture (Kuroshima)	0.0927	1.4074	15.2	LB	223	Koseki and Catholic church records, followed (average) 15 years, deaths before age 20
Schull and Neel [7]:						
Hiroshima Prefecture	0.0875	0.5317	6.1	SB, LB	1,697	Pregnancy registration at fifth month, followed (average) to 8 years
Nagasaki Prefecture	0.0986	0.1060	1.1	SB, LB	2,608	
Schull and Neel [26]:						
Kure	0.0929	0.0405	0.4	LB	564	Pregnancy registration at fifth month, followed (average) to 15 years
Yanase [27]:						
Fukuoka Prefecture:						
Hs	0.0962	1.2535	13.0	SB, LB	277	Household survey, deaths before 6 years
Hi	0.1292	0.3308	2.6	SB, LB	304	
Ta-Ko	0.0916	0.9884	10.8	SB, LB	301	
Fujiki et al. [28]:						
Yamaguchi Prefecture:						
Mis	0.1222	0.3287	2.7	SB, LB	497	Koseki records plus household interviews, followed (average) to mid-childhood
Nuw	0.1985	—0.8107	—4.1	SB, LB	234	
Kur	0.1936	—0.9608	—5.0	SB, LB	79	

TABLE 1 (*Continued*)

Investigator and Locale	*A*	*B*	*B/A*	Data Base	Size of Inbred Sample	Ascertainment
Nagano [29] (table 14; see also Yamaguchi et al. [30]): Fukuoka Prefecture (Fukuoka City) ...	0.0873	0.6765	7.8	LB	5,953	Through elementary and junior high school students and municipal administrators followed through age 12
Schull et al. [1]: Nagasaki Prefecture (Hirado)	0.1157	0.7703	6.7	SB, LB	6,626	Household survey, nonaccidental deaths largely through age 20
Freire-Maia et al. [9]: Japanese immigrants in Bauru, State of São Paulo, Brazil	0.1378	0.6995	5.1	AB, SB, LB	105	Household survey, subjects followed through age 21
Average	.1036	.6700	6.7	...	...	...

NOTE.—LB = live births; SB = stillbirths; AB = abortions.

ing the convenient B/A ratio of Morton et al. [21], where B is the coefficient of regression of mortality on percentage of inbreeding, and A is the intercept at $F = 0$. Since A includes nongenetic as well as genetic deaths, one must be very cautious in comparing two B/A ratios when infant and childhood mortality is substantially higher for one group than another. This caveat becomes especially important when we consider the results of studies on non-Japanese populations (see below). The table also indicates the data base for each sample and an estimate of sample size in terms of number of children born of consanguineous parentage, it being understood that the controls ($F = 0$) usually exceed in numbers the total inbred sample.

The B/A ratios in the Japanese studies range from a high of 15.2 to a low of —5.0. The extreme values are based on relatively small, rural populations. The high of 15.2, from a study by Schull et al. [25], involves an island (Kuroshima) with a large Catholic component; the consanguineous marriages among Catholics tended to be of low degree, so that this estimate is heavily weighted by children from marriages with a low F value. On Hirado, the socioeconomic status of Catholics was below that of Buddhists. If the same is true for Kuroshima, this estimate contains an obvious source of bias. The low estimate of —5.0 is based on a small sample from a Buddhist farming community [28] where, as in Hirado, the consanguineous marriages may have enjoyed a higher socioeconomic status. However, the larger studies [1, 7, 22, 23, 26, 29] have yielded very similar values of 5.7–7.8, save for those from Nagasaki and Kure which are nearer 1. Except for the present study

and that of Watanabe [22], these larger studies utilize urban populations, in which, on the basis of the findings in Hiroshima and Nagasaki, one would expect the children of consanguineous marriages to have a lower socioeconomic score than the controls. Thus, a correction of the B/A ratio for socioeconomic bias in these studies might be expected to reduce it, but there is no basis for an objective correction. A simple unweighted average of the result of all of these studies yields an A value of 0.1036, a B value of 0.6700, and a B/A ratio of 6.7. Alternatively, simply averaging the B/A ratios yields a value of 4.1. As noted, to an extent which cannot be specified, this value is probably inflated by socioeconomic biases. Among the conceptuses of a first-cousin marriage the average loss of zygotes subsequent to the seventh lunar month would in all these studies be about 4% greater than in controls.

Unlike some of the earlier efforts to interpret inbreeding effects (cf. [21]), the more recent attempts (see below) develop their argument, not from the B/A ratio, but from the actual inbreeding depression for a specified consanguinity class. It thus becomes important to determine the total effects of consanguinity and parental inbreeding on zygote loss following fertilization. In general, the term "stillbirth" in the various Japanese studies identifies a loss subsequent to the sixth lunar month, although in the study of Schull and Neel [7] it includes losses subsequent to the fifth lunar month. There is, however, in the Japanese studies, a very serious lack of data on early losses (e.g., prior to the fifth lunar month). The only Japanese study embracing "all recognized pregnancies" is that of Tanaka, Ohtsuki, and Furusho on two rural villages [31]. In the total material (all consanguinity classes) there were only 4.6% "prenatal deaths." This decreased insignificantly with inbreeding of the fetus (K population: $A = 0.0345$, $B = -0.0256$; U population: $A = 0.0749$, $B = -0.5158$). Thus inbreeding of the fetus of 0.06 would at face value decrease this type of mortality by 0.15 and 3.09% in the two populations. In the study of Freire-Maia et al. [9] on Japanese in Brazil (see table 1), the abortion (?plus miscarriage) frequency was 3.8% for the total material, with a nonsignificant increase in the inbred amounting to 4.0% in the conceptuses of first cousins.

The collection of accurate data on fetal loss is notoriously beset with many difficulties. In one carefully followed series where the primary objective was data on fetal loss, 24% of pregnancies reaching 4 weeks' gestation terminated in fetal loss [32]; in a second series, the total loss from conception was estimated as 29.5% [33]. A different type of data results from the studies of Hertig and associates on 34 embryos within the first 17 days of development recovered from women undergoing hysterectomies [34, 35]. Of these, 10 were so grossly abnormal that it seems almost certain the pregnancy would not have gone to term. The resulting estimate of fetal loss (29.4%) is of course minimal, since some portion of the normal-appearing fetuses may be presumed to be subject to later loss. Most of these losses would probably not have been recognized by the women. A standard caveat to the data is of course that the conditions prompting hysterectomy may have contributed to the abnormalities of development. There is obviously gross underreporting in this Japanese material.

Some further guidance on fetal loss can be obtained from the results of studies on Negroid and Caucasian populations. As summarized by Krieger [18], in eight studies, the A value (intercept) ranges from 0.091 to 0.173, the B value from -1.111 to 1.885, and the B/A ratio from -7.41 to 19.88. We shall not attempt to adjudicate between these studies, but settle for an average A of 0.1227, an average B of 0.3935, and a B/A ratio of 3.2, or 4.5 if we average the individual B/A ratios. In the face of the much lower abortion and miscarriage rates in the two Japanese series quoted above, the propriety of applying these rates to Japanese populations can be contested, but in order later to undertake certain preliminary calculations, we shall do so. These results suggest that the excess loss of zygotes from conception to the seventh month of gestation in offspring of first-cousin marriages as contrasted with nonconsanguineous is 2.4%; the fragmentary Japanese data suggest lower values. If, however, only half the losses are being reported, as seems possible from the previously quoted data of French and Bierman [32] and Erhardt [33], the loss of conceptuses in a first-cousin marriage may be 29%–30%, where expectation in the controls is taken to be 25%. This is the provisional figure we feel forced to use. Obviously, should the true frequency of fetal loss be 50%, a figure readily derived by combining the early-loss data of Hertig et al. [34, 35] with the data on predominantly later losses of French and Bierman [32] and Erhardt [33], then the inbreeding depression of this indicator would be proportionately greater. This is clearly the weakest aspect of the data at present.

Earlier we mentioned the occurrence of significantly fewer childless marriages in consanguineous unions on Hirado. Tanaka et al. [36] report a similar significant finding in two adjacent rural communities in the southern district of Fukuoka Prefecture, Kyushu. It is not clear whether this is sociological or physiological in origin. The latter would be due to a lesser "incompatibility load," as first defined by Stern and Charles [37]. The data of Tanaka et al. [36] are highly influenced by one aberrant group; in certain calculations to follow we will employ our own more consistent data.

There are of course far fewer data available on parental inbreeding effects than on parental consanguinity effects. Aside from our own, the only data on Japanese are those of Tanaka et al. [31], wherein the excess "prenatal" mortality in the children of mothers with a coefficient of inbreeding of 0.0625 was 0.3% in the K population and 2.3% in the U population. The regressions in question were nonsignificant; the values are in the range of those in the present study. It must be noted that Tanaka's and our studies cover different but overlapping portions of the conception-to-reproduction span. For working purposes, we will entertain a preliminary figure of a 2% excess zygote loss prior to the age of reproduction among the conceptuses of women who are a product of a first-cousin marriage. There do not seem to be supplementary data from Caucasian populations. We note that the Hirado consanguinity effects are very close to the average of all these studies to date in Japan, a fact which strengthens the case for generalizing from the Hirado findings on maternal inbreeding effects.

We come now to an effort to develop an estimate of total zygote loss as a result

of a first-cousin marriage. This estimate, to reiterate briefly, must reflect the following: (1) the diminished frequency of "childless marriages" among consanguineous unions; (2) possible fertility differences between consanguineous and nonconsanguineous marriages not explicable in terms of the differences in "childless marriages"; (3) the increased zygote loss between conception and 7 months of gestation in the consanguineous marriage; (4) the increased loss of inbred fetuses which survive 7 months of gestation between that age and reproductive maturity; and finally (5) an adjustment for parental inbreeding. Table 2 sets out the impact

TABLE 2

TOTAL ZYGOTIC LOSS TO BE EXPECTED AMONG FOUR COHORTS OF MARRIED WOMEN, TWO MARRYING THEIR FIRST COUSINS, TWO MARRYING UNRELATED MALES

	UNRELATED MARRIAGES		FIRST-COUSIN MARRIAGES	
	Wives Not Inbred	Wives Proportionately Inbred	Without "Reproductive Compensation"	With "Reproductive Compensation"
Total marriages	100,000	100,000	100,000	100,000
"Childless marriages"	9,000	9,000	5,000	5,000
Fertile marriages	91,000	91,000	95,000	95,000
Total conceptions	455,000	455,000	475,000	502,550*
Early fetal loss	113,750 (25%)	113,750 (25%)	137,750 (29%)	145,840 (29%)
Survivors to 7-months gestation	341,250	341,250	337,250	356,710
Deaths in subsequent years but prior to age 21	34,125 (10%)	34,800 (10.2%)	47,890 (14.2%)	50,650 (14.2%)
Survivors to adulthood	307,125	306,450	289,360	313,050
Zygotic loss (%)	32.5	32.7	39.1	39.1
Mean number of surviving conceptions	3.07	3.06	2.96	3.13
Mean number of wasted pregnancies	1.48	1.49	1.86	1.96

NOTE.—The magnitudes of the various effects which contribute to differences between these cohorts are based upon the Hirado Health Survey.

* The first-cousin marriage is assumed to produce 5.30 offspring, on the average, as a result of "reproductive compensation," as contrasted with five offspring in the absence of compensation.

of these various effects upon four cohorts of women, two marrying unrelated males and the other two their first cousins. The magnitudes of these effects are assumed to be equal to the estimates derived from the various studies on Japanese, with special reference to the Hirado Health Survey where other data are missing or conflicting. Results are rounded to the nearest percentage point generally. Thus, 9% of marriages of unrelated spouses are assumed to be childless whereas only 5% of first-cousin marriages are. We assume the mean number of conceptions in the marriage of fertile unrelated spouses to be five. One in four of these latter conceptuses fails to survive the first 7 months of gestation, and 29% fail to survive in the marriage of first cousins. Our data suggest that on the average, the fertile first-cousin marriage produces 0.29 conceptuses more than the nonconsanguineous mar-

riage, that is, 0.047 ± 0.011 conceptuses per percent consanguinity (see [4], table 7). We further assume that maternal inbreeding does not affect early fetal loss but does diminish survival prospects after 7 months of gestation, an assumption which is not wholly acceptable, but there are insufficient data to argue otherwise. The various values cited above are admittedly somewhat arbitrary but they accord well with the Japanese experience, findings on early fetal loss in studies in New York and Hawaii, Krieger's [18] summary of early fetal loss from consanguinity in a variety of populations, or appear to be reasonable extrapolations from these sources.

Granted these assumptions and the mortality values discussed earlier in this section, we find that net zygotic loss in the first-cousin marriage is 39.1% as contrasted with 32.5% in the unrelated marriage. These values are predicated on the assumption that some 10% of women who marry their cousins are themselves the products of first-cousin marriages, but none of the women marrying unrelated spouses are. If, by contrast, we assume that the probability that a woman will marry her cousin is independent of whether her parents are related to one another, and examine the reproductive performances of two cohorts of women equally inbred, then the net zygotic loss in the first-cousin marriage is 39.1% as compared with 32.7% in the unrelated marriage. Relative zygotic loss, however, constitutes only a partial picture of the impact of the first-cousin marriage; one needs to examine also the absolute loss as well as the mean number of conceptuses which survive to the age of reproduction. Table 2 sets forth these means for the following cases: cohorts of (1) noninbred women married to unrelated spouses; (2) women, one in 10 of whom is inbred but all are married to unrelated spouses; (3) women, one in 10 of whom is inbred and all are married to their first cousins without "reproductive compensation"; and (4) women, one in 10 of whom is inbred, and all are married to their first cousins with "reproductive compensation." We note that despite a relative advantage of as much as 20.3% in zygotic wastage, the relative advantage of the unrelated marriage in mean number of surviving progeny may be no more than 3.5%, and, in fact, consanguineous marriages may enjoy an advantage of as much as 2.2% in the presence of "reproductive compensation" under the circumstances here outlined. Clearly, small fertility differentials can produce profound effects in man.

A question which is highly relevant to efforts to utilize the results of consanguinity and inbreeding studies to reach inferences concerning the genetic structure of human populations is the extent to which these effects are related to disease pressures. In a sample where all survive to the age of reproduction, or all die before that age, there can be no demonstrable consanguinity effects on mortality. Intuitively, one suspects there is some mortality base at which consanguinity effects are maximal, but this base cannot now be specified. The extensive clinical data from this study and the Hiroshima-Nagasaki study are in truth of little value in this respect, in that except for the category of severe congenital malformations [38], it is not feasible to relate the increased frequency of medical defects to probabilities of survival under other (harsher) conditions. We note, however, the similarity of

the *A* term in the various Japanese studies. Give or take a few percentage points, about 10% of the various samples of neonates have died at the time of the study. This fact must be borne in mind whenever the Japanese findings are compared with those on other ethnic groups; somewhat different conclusions might result from a mortality base of 20%, 30%, or even 40% instead of 10%.

C. SOME THOUGHTS ON REPRODUCTIVE COMPENSATION

The preceding section introduced the concept of reproductive compensation, the genetic significance of which was first recognized some 30 years ago by R. A. Fisher (see [39]), who suggested that the replacement of a child that dies young might be instrumental in the maintenance of the genetic variability observed in the Rh blood-group system. This suggestion precipitated a controversy which still continues (reviewed in [40]), and has tended to confuse the general concept of reproductive compensation with the role it may or may not play in the Rh polymorphism. This has had the unfortunate effects of limiting interest in, and wider recognition of, reproductive compensation as a means to maintain genetic variability, or at least to dampen the rate of its reduction by selection in man.

Data on the existence of reproductive compensation in a context more general than the Rh blood-group system are sparse; they have recently been summarized by Reed [40]. Only Newcombe [41] appears to have searched directly for evidence that the occurrence of a child who is stillborn or succumbs early in life influences the subsequent reproductive performance of that child's parents. He examined the fertility of parents in the 4 years immediately following the birth of a stillborn child or one dying from erythroblastosis, hemorrhagic disease, Down's syndrome, or asphyxia. Only for one of these four conditions, namely, Down's syndrome, was there evidence of an elevated maternal fertility. The numbers available for study were small, the span of reproduction studied short, and as a consequence other slight but biologically significant effects could not be precluded. More studies of this general nature are to be encouraged, for as we have pointed out elsewhere [4], the opportunities for reproductive compensation are already enormous and can only increase as family planning and limitation become more widespread. Two observations lend strong support to this assertion. First, the bulk of prereproductive mortality in developed as well as developing nations has been and continues to be ascribable to deaths in the first year of life; most, if not all infantile deaths are potentially replaceable. That is to say, the parents of the deceased child will generally still be of ages compatible with further reproduction. Second, even in highly prolific groups such as the Hutterites or the Amish, mean family size is still well below man's apparent reproductive potential; thus, unused reproductive opportunities appear to exist in virtually all human populations.

A strong case for genetically significant compensation is difficult to establish, for it requires evidence from a single population of genetic selection, a phenomenon which is itself difficult to document, and of replacement of those individuals whose genotype (phenotype) leads to their early elimination from that population. In the strict sense, "proof" of genetic compensation requires "disproof" of the hypothesis

that some unrecognized factor causes a correlation between death rate and family size. Circumstantial evidence in support of compensation may be more readily obtained; a case in point are the observations from Hirado to which we now turn. Among marriages contracted in the years 1920–1939, it can be established that (1) mortality among liveborn offspring increases with increasing parental consanguinity, and (2) the consanguineous marriage is more fertile as measured either in terms of total pregnancies or total live births. Indeed, the added fertility is sufficient to offset the increased risk of premature death among the offspring of related spouses; that is, the number of children surviving to adulthood in the consanguineous marriage is as large as that associated with marriages of unrelated individuals. If this increased mortality is due to increased homozygosity, as is presumably true, then the increased reproduction must at least dampen the elimination of those genes which in homozygous form are lethal, since there will be two chances in three that each surviving replacement conceptus will be heterozygous for the "disadvantaged gene." The analyses on which the findings cited rest attempt to take into account, either through classification or covariance analysis, possible differences in mortality and fertility ascribable to parental occupation, socioeconomic status, year of birth (or length of marriage), year of marriage, etc. There is no evidence that the findings are explicable on any of these grounds.

Several other supportive lines of evidence concerning reproductive compensation on Hirado are now available. It can be shown, for example, that on Hirado the number of months intervening between the birth of a child succumbing in the first year of life and the birth of the next child is smaller, on the average, than the number obtaining with respect to live births not succumbing, the difference amounting to more than 10 months. This shorter interval is largely independent of the birth rank and sex of the dead child. Thus irrespective of a child's place in the sibship, if death occurs in the first year of life, the waiting time to the birth of the next child is shorter than the expected waiting time based upon liveborn infants surviving at least 1 year. Though the evidence is more limited, the same appears to be true for intervals following the births of stillborn infants. These findings are neither unique to Hirado nor Japan; indeed, such differences are assumed to exist in most current models constructed to describe the distribution of observed birth intervals (see, e.g., [42, 43]). We further find, however, that this foreshortening of the birth interval following an infantile death holds, and approximately equally, for intervals associated with related as well as unrelated marriages. Thus, the waiting time following the birth of a child destined to die in the first year of life, whether biological or sociological in origin, is the same or certainly nearly so for the consanguineous and nonconsanguineous marriage. If the motivation and capacity to replace an infant dying young is invariant with parental relationship, the increased fertility of the consanguineous marriage may simply reflect the increased opportunities for replacement due to increased infant mortality. There are a number of assumptions implicit in this remark. One is, of course, that the distributions of reproductive spans in the consanguineous and nonconsanguineous marriages are the same, that is, each has the same length of time into which to intercalate births.

A second is that little or no birth control has been practiced by couples on Hirado. While it seems highly unlikely that no birth control was practiced in the years from which these data stem, the control may have been limited. It is generally accepted that in societies practicing little or no birth control, average birth intervals may vary from approximately 24 months to somewhat less than 36 [43]. The Hirado values fall within this range.

Recently, Reid [44] has described observations from South India similar to those from Hirado. He has interpreted these observations somewhat differently; he attributes the increased fertility of the consanguineously married to reduced domestic stress rather than compensation for increased infant mortality. It is important to note, however, that for the effect of consanguinity to be linear on F, as it is, reduction in domestic stress must be proportional to the biologic relationship which exists between husband and wife. While this assumption of linearity of stress may be difficult to document, it seems no less ponderable a proposition than the original assumption of less stress to the consanguineously married.

The opportunities for reproductive compensation may of course have been decidedly less in the high-mortality, high-fertility societies of the past several thousand years than on twentieth-century Hirado, where completed family size is about two-thirds that of some primitive agriculturalists. If the former pattern had been characteristic of all human evolution, then reproductive compensation, while possibly pointing the way to future changes in the frequency of certain genes, would have had little or no impact on present-day gene frequencies. However, deliberate child spacing, accompanied by relatively low infant and childhood mortality rates, was characteristic of many primitive societies. In the last resort, this "child spacing" was accomplished by infanticide, especially directed toward deformed infants. In one relatively unacculturated tribe of South American Indians where it was possible to study pregnancy rates not only by history but by physical examination and the occurrence of chorionic gonadotrophins in the urine, the average interval between the birth of children permitted to live was estimated at 4–5 years [45, 46]. It has been suggested that one of the early, significant milestones in human evolution was the development of parental care to the point where the resulting rate of entry of new life into the culture threatened its stability, and crude means of population control were introduced [45]. These inhibitions were lost when the Agricultural Age both lessened the need for mobility and increased the demand for family labor. If this viewpoint is correct, then reproductive compensation may indeed have influenced the present-day frequency of certain genes.

Granted that reproductive compensation does occur on occasion, possibly even frequently, it becomes of some moment to determine the consequences of such compensation upon gene, genotype, and phenotype frequencies. Almost all efforts to date to appraise the possible effects of replacement involve single loci and discrete time models. Even here, simple answers may not follow, for as Edwards [47] has pointed out, the inclusion of compensation into gene-frequency models leads to nonlinear recurrence relationships, and the latter can pose formidable analytic problems. Suffice it to state that under some fairly simple genetic formulations,

compensation or overcompensation can be shown to stabilize gene frequencies at polymorphic proportions [48, 49]. The impact of reproductive replacement upon more complex models, such as those which envisage threshold selection with or without linkage, can only be perceived intuitively, and then but dimly. However, as previously intimated, it is possible to appraise the effects of reproductive compensation on some simpler models. Motulsky et al. [50], for example, have considered the effect of full replacement on the rate of elimination of a recessive lethal previously but no longer maintained by heterozygote advantage, and find that the rate of decline (ignoring mutation) would approximate $2/3\ q^2$ rather than the q^2 expected in the absence of compensation, where q is the frequency of the recessive lethal gene. The Hirado situation appears to approach that of full replacement. If the gene had reached high frequencies because of heterozygote advantage, if compensation occurred, and if the heterozygote advantage also persisted, at equilibrium, carriers of the lethal gene would be 50% more common than at equilibrium in the absence of compensation. Failure to recognize the existence of reproductive compensation could in both instances lead to overestimation of mutation rates through faultily ascribing the higher-equilibrium gene frequencies which will obtain to fresh mutations. All of the effects just cited are small, but of potential evolutionary significance.

D. THE INTERPRETATION OF INBREEDING RESULTS

The initial efforts at the utilization of data on the results of consanguinity and inbreeding in man to illuminate the genetic structure of human populations were directed toward the estimation of the number of lethal and deleterious genes possessed by the average individual [51–56]. These calculations, greatly handicapped by the limited data, were not concerned with the type of genetic system which these lethal and deleterious genes were segregating and assumed, in the case of lethal effects, that the effects were due to the segregation of unconditional lethals.

The paper by Morton et al. [21] thus constituted a milestone, since it attempted to develop arguments based on the magnitude of the inbreeding depression concerning the extent to which the inbreeding depression was based on homozygosity of genes from "classical" systems (a "mutational" load) and homozygosity from the genetic polymorphisms (a "segregational" load). A key assumption in this formulation was the concept of a multiplicative genetic load, that is, that each set of alleles could be cost-accounted separately, with the probability of survival then given by $(1 - s)^x$, where s is the probability of death from segregation at a particular locus, and x the number of loci segregating. The concept was introduced of "lethal equivalents," later extended to "detrimental equivalents" [57]. This concept assumed that the inbreeding depression produced by a single recessive lethal gene might also be produced by two genes with half-lethal effects, four genes with quarter-lethal effects, etc. There was thus implicit the assumption of independence of genetic effects in this sphere.

Elsewhere we and others have reviewed in some detail the reasons why, especially at the low B/A ratios observed in human populations, this ingenious approach will

fail to yield decisive insights [7, 58–60], a fact also recognized by Crow [61]. The even lower B/A ratios which obtain if we are, for reasons discussed above, guided more by the results on Japanese than on Caucasians, only reinforce that conclusion. There seems no need to pursue the matter further.

At the same time that a vigorous discussion concerning the insights provided by this formulation when B/A ratios were low was in progress, experimental data were creating a different sort of difficulty for the formulation. The investigations of numerous persons, aided by the ready availability of cheap electrophoretic techniques for the recognition of protein variants, revealed that the genetic polymorphisms were far more common than previously suspected. It quickly became apparent, as additional polymorphisms were recognized, that if these polymorphisms were maintained by selection, then with a multiplicative system of cost accounting and reference to some optimum genotype, the "load space" of the human species was in danger of being exhausted long before the end of the polymorphisms was in sight [62].

The principal general responses to this development have been of three types. (1) A substantial effort has been directed toward the theoretical possibility that, given a finite population, many of the genetic polymorphisms (and the gene fixations which with a finite probability result from them) might not be maintained by selection but by the pressure of mutation resulting in alleles which are neutral (i.e., alleles whose phenotypic effects are selectively equivalent to the standard allele) [63–66]. (2) The possibility has been emphasized that at any one time only a small proportion of the polymorphisms is the subject of active selection, the remainder being a legacy of the past [67]. (3) Finally, the possibility that the conceptual framework was incorrect began to receive increasing attention. As long ago as 1951 one of us pointed out that the concept of "one mutation—one genetic death" was misleading, that the death of a single individual could remove a number of deleterious mutants from the population [68]. In 1967 three different papers appeared demonstrating that if selection were envisioned as directed at the most disadvantaged tail of a continuously distributed spectrum of fitness, that is, if selection were proportional and involved a threshold which could shift with both genetic and environmental circumstances (Wallace's [69] concept of "hard" and "soft" selection), then the number of polymorphisms which could be maintained was much greater than with the previous formulation [60, 70, 71]. For instance, King [70] calculated that at a zygote loss of 50% prior to reproduction, and with an inbreeding depression in the offspring of first cousins of 4.5% (compatible with our findings if half the observed depression is due to segregation from classical systems), then 500 independently segregating polymorphisms each with a selective advantage of 0.005 in the heterozygote could be maintained. Under the previous formulation, the probability of survival in this situation (gene frequencies of .5) would be approximately $(0.995)^{500}$, or 0.0816, that is, it was clearly impossible to maintain by selection the number of polymorphisms it was becoming necessary to postulate. With the concept of proportional selection, the calculation of "lethal or detrimental equivalents" (as opposed to genes) becomes so much more com-

plicated as to become impractical, since one must always make the computation with reference to the point on the scale of zygote survival which the population under consideration exemplifies.

The first round of these new formulations neglected the obvious complications introduced by the interaction of selection with linkage. The initial efforts to understand the complications which linkage introduces into attempts to formulate selective pressures involved relatively simple models (e.g., [72–74]). Significant steps toward integrating the concept of proportional selection with the probability of close linkage between the loci responsible for polymorphisms have now been taken by Wills et al. [75] and Franklin and Lewontin [76]. It is clear that linkage creates "super-genes" in which, with the proportional model, the selective pressure on any individual allele is less than if a multiplicative model with independent assortment is visualized. The possibilities for persistence of these "super-genes," especially with the maintenance of linkage disequilibrium through selection, had not been previously appreciated. Franklin and Lewontin [76], utilizing the estimate that 40% of all structural genes are polymorphic in *Drosophila pseudo-obscura*, calculate that if there were no more than 5,000 loci in this species and a total map length of 250 centimorgans, there would be eight polymorphic loci per centimorgan. With the lack of recombination in male Drosophila, the average recombination fraction between adjacent polymorphic loci under these assumptions would be only 0.0006.

The concept of proportional or threshold selection, together with the facts of linkage, thus provide a conceptual framework within which a great deal more nonneutral genetic variation can be accommodated than under the earlier formulations. In recent years, considerable effort has been expended by the proponents of the view that a large proportion of the genetic variation of polymorphisms is neutral, in the demonstration that in a finite population even with neutrality a mutation could achieve polymorphic frequencies and even go to fixation. We propose now to use the data on consanguinity and inbreeding effects to show that selection could be maintaining a very large number of polymorphisms in man. We cannot emphasize too strongly that the demonstration, especially in this complex field, that a set of facts can be made to appear consistent with a hypothesis in no way constitutes proof. We claim no more for this demonstration than that, with all its oversimplifications, it is thought provoking.

Wills et al. [75] have demonstrated that in a computer model in which selection is at the level of the total phenotype of an organism with a single chromosome of 100 centimorgans, and linkage and recombination are included, a high percentage of polymorphism can, following a period of relatively severe selection, be retained in populations of size as low as 100, even with very low selection pressures (5% per chromosome per generation). Let us see where utilizing our own data for such a calculation leads us. The evidence suggests that in man, approximately 50% of all zygotes in any one generation fail to contribute to the next generation. The evidence is further compatible with the loss of an additional 6%–7% of all zygotes in the offspring of a first-cousin marriage subsequent to conception. Let us assume

half of this loss to be due to genes resulting from recurrent mutation and the remainder to segregation from balanced polymorphisms. (This does not assume that all polymorphisms are maintained by selection.) The matter of reproductive compensation need not enter into this particular calculation. Recall that all human populations in which consanguinity effects have been studied are expanding, which lowers the estimate of the inbreeding depression from that to be observed in a stable population. Thus, a "true" selection pressure due to polymorphisms of 5% per chromosome under random breeding—which Wills et al. [75] have shown could maintain (conservatively) 200 polymorphisms per chromosome—might measure at 3% per chromosome in an expanding population. Ignoring the complications introduced by crossing-over, in the offspring of a first-cousin marriage the loss increases to approximately 3.2% per chromosome. Then whereas in the outbred population the proportion of survivors is $(0.97)^{23} = 0.4963$, in the children of a first-cousin marriage it becomes $(0.968)^{23} = 0.4733$ (the discrepant contribution of the sexes is ignored). The calculated inbreeding depression from 4,600 polymorphic loci maintained by selection is clearly within hailing distance of the observed facts. The possibility that even larger numbers of polymorphisms might be supported by selection with proper chromosomal organization is strongly suggested by Franklin and Lewontin [76].

Should one choose to fiddle with this model, he could of course produce a much better fit. This would prove nothing. The purpose of this demonstration is rather to emphasize that just as one can elaborate on how much of the observed genetic polymorphism of man can be accounted for if few of the polymorphisms are involved in active selection, so it can also be accounted for if a rather large number is so involved. The present state of our conceptualization and data simply do not permit hard inference.

Elsewhere we have itemized the more promising approaches to the strategy of deciding whether the genetic material is as loosely organized as follows from the view that most variation found in polymorphic proportions in populations is neutral, or whether in fact this variation will in time be found to have a structure maintained for the most part by selective processes [77]. We do not see the further study of consanguinity and inbreeding effects as particularly helpful in reaching this decision, aside from the possibility that in areas where uncle-niece marriages are relatively frequent, some data may become available concerning the question of synergism of gene action in man. On the other hand, such studies do remain one of the strong approaches to the investigation of reproductive compensation.

E. A COMPARISON OF CONSANGUINITY AND INBREEDING EFFECTS WITH OUTBREEDING EFFECTS

The principal effects of outcrossing on morbidity and mortality which are currently envisioned are due either to differences between the F_1, F_2, etc., and the parental stocks in the frequency of homozygosity for specific genes or to loss of genetic coadaptation [78] in the hybrid populations. With respect to the first of these considerations, the effects of outbreeding are the obverse of inbreeding. As is

well known, given a recessive gene with differing frequencies in two populations, the frequency of the homozygote in an F_1 derived from equal numbers of these populations will be closer to the frequency in the population in which the gene is less frequent than to the frequency in the other population. The magnitude of this effect is a function of the two gene frequencies. If, further, in one human population there is a series of loci at which recessive deleterious alleles are found in relatively high frequency, and in the second population another series of loci at which there are other recessive deleterious alleles in relatively high frequency, the hybrid population will exhibit a lower frequency of death and defect, insofar as it is controlled by these alleles, than either parent population. The total effect of outcrossing on monofactorial qualitative traits, then, depends to a large degree on the extent to which alleles with homozygous recessive effects have differing frequencies in the two populations involved.

In an earlier section, we discussed the thesis that much selection is directed toward individuals who fall in the tail of a continuously distributed range of viability. Genetic death, then, may often be considered a quasi-continuous trait, that is, a trait to which the predisposition is essentially continuously distributed in the population, the phenotype appearing when some threshold of predisposition is exceeded. Falconer [79] has summarized the statistical arguments for hybrid vigor in continuously distributed traits. The extension of this argument to multifactorially inherited quasi-continuous traits is simple and straightforward and need not detain us here.

Although much remains to be learned, it is already apparent that the major races of man differ widely in the frequency of the genes found at certain specific loci. A tabular summary illustrating this point with respect to some of the well-known genetic polymorphisms as they occur in Caucasoids and Mongoloids is to be found in Morton et al. [80]. The gene frequencies for some of these "polymorphisms" (Diego, Rh, Duffy, Gm) vary to such an extent in major ethnic groups that if they are subject to selection, the kinds of outcrossing effects just discussed might under certain reasonable assumptions be expected to obtain.

With respect to the less common "recessive" genes, the evidence that populations may differ in the frequency of the alleles found at specific loci is of two types, direct and indirect, and in either case must still be considered preliminary. The indirect comes from estimates of gene frequencies based on consanguinity effects. Thus, of five recessively inherited traits occurring in Japanese and European populations, for which semisatisfactory data were available on the frequency of first-cousin marriage in the parentage (on the assumption of a single locus permitting a calculation of gene frequency), for one (xeroderma pigmentosum), a higher frequency of the gene in Japanese seems very likely, whereas for four (albinism, infantile amaurotic idiocy, ichthyosis congenita, and congenital total colorblindness), there is no suggestion of any important difference [81].

An important difficulty with the indirect approach is the degree to which the uneven distribution of gene frequencies and intensity of inbreeding within given geographic areas may obfuscate the calculation, resulting in what we have termed a

"neighborhood effect" ([82]; see also [83]). Another difficulty is uncertainty as to whether there are several different loci characterized by recessive alleles producing the phenotype in question. Thus, the data on xeroderma pigmentosum are also consistent with the hypothesis of the same phenotype frequency in the two groups, only with one or a few genes involved in the Japanese but more numerous genes in Caucasians. However, this type of difference would also be reflected in hybridity effects. In this connection, the data on the results of marriage between congenital deaf-mutes from Northern Ireland [84] and from Denmark [85], as analyzed by Chung et al. [86], suggest that in the former area there are, on the assumption of equal frequencies of each of the genes contributing to the phenomenon, 36 ± 12 noncomplementary recessive genes (at some unknown number of loci) whereas in the latter there are 6 ± 2 noncomplementary recessive genes. This would seem to point to marked genetic differences between two rather closely related Caucasoid groups. However, Chung and Brown [87], using the analytic techniques of Chung et al. [86], find the data from the United States to be consistent with an estimate of five genes. In view of the larger Irish than Danish component in the ancestry of the present U.S. population, one would expect a figure for the United States closer to that for the Irish. Possible explanations for the discrepancy are the "neighborhood" effect mentioned above, differences in diagnostic criteria between the sets of data involved, or a great sensitivity of the method to its assumption and minor perturbations in the data. Although for the sake of the argument we are developing we would like to believe such a difference exists, we find it not proven.

There is also growing direct, observational evidence for the uneven distribution between ethnic groups of normally "recessive" genes. For instance, cystic fibrosis of the pancreas, due to homozygosity for a recessive gene, occurs among not less than one in 10,000 Caucasian infants, and perhaps as often as one in 4,000, but is much rarer in Negroes, Orientals, and Indians [88–91]. The gene-producing acatalasemia is not only largely restricted to Mongoloids but even within one of these groups, the Japanese, shows a quite uneven distribution (reviewed in [82, 92]). Fructosuria and pentosuria seem largely traits of Ashkenazic Jews of East European extract (reviewed in [93, 94]). Thalassemia major of the β-chain type is certainly less common in the peoples of northern Europe than in the circum-Mediterranean peoples (reviewed in [95]). The recessive gene responsible for familial Mediterranean fever seems largely restricted to Armenians and Sephardic Jews [96]. Finally, the restricted ethnic distribution of homozygosity for the genes responsible for hemoglobins S, C, and E is abundantly established. We conclude, then, from the arguments above and the data just cited, that the growing information on population structure leads to the expectation of a decrease in the frequency of recessively inherited phenomena in human hybrid populations. From the arguments advanced above, there should also be a decrease in the frequency of the quasi-continuous traits in hybrid populations, but unlike the case for monogenic inheritance, it is not now possible to begin to develop the discussion in terms of specific entities.

There is, as mentioned at the beginning of this section, a second set of data and

theory relevant to the expectations of outcrossing. As brought out in Section C, increasingly selection is visualized as operating on the phenotype resulting from favorable combinations of linked genes. There are experimental data consistent with coadapted or integrated genetic structure in such diverse animals as Drosophila and the frog. To the extent that homologous chromosomes can be envisioned as functionally "super-genes," overdominance effects could be lost in the F_1 and the advantage of intrachromosomal integration lost in further generations as a result of crossing-over. Thus the total impact of hybridization in theory represents a balance between the loss of coadaptation and alteration in the frequencies of specific genes.

When human population structure is better understood, there should be a predictable relationship between the results of inbreeding and outcrossing. For the present, however, we must be content with cautious comparisons. Unfortunately, difficult though extensive and careful studies of inbreeding have been, proper studies of the effects of outbreeding on morbidity and mortality face even greater difficulties. There are, in fact, only three recent attempts to evaluate the effects of outcrossing on those indicators of inbreeding effects, such as mortality and congenital malformations, studied so extensively in Japan.

The first of these efforts is that of Saldanha [97, 98] in Brazil, utilizing either the records of a pediatric public health clinic or hospital births. Evaluation of the data is rendered difficult by the lack of information on the socioeconomic comparability of the various groups, and, for the former data, somewhat uncertain denominators in the frequency calculations. In the clinic data, among Caucasoid groups there appeared to be less congenital defect among the children with the most heterogeneous ethnic backgrounds, but this could also reflect differences in survival and the factors resulting in clinic visits. Among the hospital series, no differences in the collective frequencies of a variety of malformations were seen among children born of Caucasian, mulatto, and Negro parentage.

The second of these studies was carried out in Hawaii by Morton et al. [80]. Although the locale for this study is without doubt one of the most favorable sites in the world for such studies, there were nevertheless extensive socioeconomic differences between ethnic groups and derivative populations, involving such factors as legitimacy, maternal age, occupation, urban residence, occurrence of birth in hospital, and month of first prenatal visit. Where comparisons can be made, these differences appear at least as great as those between consanguinity classes in Japan. It is not immediately clear why such differences should be considered a serious defect in the consanguinity studies in Japan (see [8]), despite the use of regression techniques, but they do not in the authors' minds impair the studies in Hawaii. Despite much material—172,448 live-birth certificates and 6,879 fetal death certificates for all births registered in the interval 1948–1958—the authors are unable to demonstrate significant outcrossing effects on the frequency of congenital malformation, early fetal death, stillbirth, infant death, or the report on the birth certificate of previous fetal or postnatal death in the sibship. This is true for major hybridity (primarily "Atlantic" populations versus "Pacific" populations) and for minor hybridity (lesser parental differences than the foregoing, such as

Chinese and Japanese). Furthermore there were no "recombination" effects, which term apparently refers to effects to be observed where outcrossing occurred some generations previously.

The third recent study on outcrossing, carried out in Rhode Island, was restricted to fetal loss (abortions and stillbirths) by Caucasian mothers in relation to country of origin of ancestors [99]. It was concluded that "fetal loss (F_1 generation) in matings of the parental generation (P_1) increases cumulatively by approximately 2.5% to 3% with each additional country of birth in the great-grandparental generation (P_3)." The results are opposite in direction to those of Saldanha [97, 98]. An attempt is made to explain the finding in terms of loss of genetic coadaptation. The possibility of a lower socioeconomic status of individuals with a higher proportion of relatively recent immigrants to the country in their background seems to us an equally likely explanation, although Bressler reports that fetal loss was (insignificantly) higher in the upper socioeconomic group. It would be strange to observe effects of this magnitude due to loss of coadaptation in minor hybridity but not in the major hybridity represented in the studies of Morton et al. [80]. The need for further observations is evident.

For the present, the bulk of the data on outcrossing effects comparable with the Japanese data on inbreeding, characterized by an effort to control socioeconomic factors, remains that supplied by Morton et al. [80]. The failure of this extensive and well-designed study to yield significant outcrossing effects raises such possibilities as: (1) the loss of coadaptation with outcrossing rather exactly offsets the effects of the changes in recessive gene frequencies which accompany outcrossing; (2) genetic coadaptation in man is an insignificant phenomenon, and the racial and populational differences in the frequency of rare and "semi-rare" genes, mentioned above, are too slight and/or too unrelated to selection to be reflected in outcrossing effects; (3) there are unrecognized confounding effects in these studies which are obscuring the outcrossing effects predicted from gene frequency data; or (4) as in the case of our own data on parental inbreeding effects, their series, because of its size, can only be used as a rough guide and not as the basis for strong inference concerning the absence of outcrossing effects in malformations or early death. Other alternatives can also be envisioned. What is clear, and important to the argument to follow, is that there is no evidence in their data for the role of recessive inheritance in any of their indicators of an outcrossing effect. The results of studies on outcrossing effects are as ambiguous as those of inbreeding effects, with reference to the relative importance of mutational and segregational loads.

In 1954, Lerner [100] coined the term "phenodeviants" for sporadically occurring morphological deviants found in inbred lines of chickens and attributed to exceeding some threshold of multiple homozygosis. Sporadic was used in the sense of occurring occasionally within the line (i.e., consistent with multiple occurrences with sibships). The necessary multiple homozygosis was postulated to arise in many ways, that is, to be relatively nonspecific. Neel [101], attempting to account for many of the epidemiologic characteristics of human congenital defects, later

suggested that some portion of these defects might correspond to such phenodeviants, a suggestion vigorously challenged by Morton ([57]; see also [6]). Lerner [100] related the homozygosis to segregation in heterotic systems, but Neel [101] suggested that the essential concept could also be fulfilled if the responsible genes were maintained in part by mutation pressure. King [70] recognized that the threshold model of selection discussed earlier was "derived directly" from Lerner's concept of genetic homeostasis. The concept that certain traits in the chicken and mouse are due to multifactorial inheritance combined with a threshold effect (quasi-continuous variation) [102, 103, et seq.] has now been extended to a variety of human diseases by Falconer [104], Carter [105], Chung et al. [106], and Woolf [107]. It seems to have been generally overlooked that this implies an effect of multiple homozygosis which can be achieved in a number of different ways! In fact, leaving aside the question of the mechanisms maintaining the responsible genes, it is difficult to perceive any essential difference between the concept of phenodeviants and of congenital defect on the basis of quasi-continuous variation, with respect to the role played by homozygosity at numerous but varying loci.

The rejoinder by Schull and Neel [7] to Morton's criticism has been followed by further criticism by Morton et al. [80] in the monograph on race crossing as well as by Mi et al. [6] in a study of malformations in northeastern Brazil. *What is at issue now is not so much the validity of the original suggestion as the question of what constitutes evidence in population genetics.* Mi et al. [6], analyzing data on congenital malformations compatible with survival in northeastern Brazil (i.e., for the most part minor) in a selected series of migratory adults and children, first demonstrate a significant consanguinity effect quite similar to that reported in Japanese material by Schull [38]. In an attempt to analyze this inbreeding effect, they apply to the data the same model applied to entities in which simple recessive inheritance can be shown by independent analysis to be involved, such as deafmutism [86] or limb-girdle muscular dystrophy [108]. This model assumes "that families with normal parents in the general population are divided into two groups: a major fraction in which the probability of a malformed child is so small that it may be assumed constant, and a minor fraction in which the malformation probability approaches 0.25, as for a completely penetrant recessive trait" (p. 181). All malformations are considered phenotypically equivalent, that is, a family in which the same malformation occurs twice is scored the same as one with two different malformations! This Procrustean approach would seem to ignore, for the sake of using a convenient analysis, all the data on the differing empirical recurrence risks for various congenital defects (i.e., the mix that might result from this approach).

If there is an inbreeding effect in the malformations concerned, the device of combining unlike defects, of course, selects for marriages in which the probability of consanguinity is especially high. The data are indeed better fitted by a double-binomial than a single-binomial distribution, proving once again the heterogeneity of congenital defect, or, as they put it, "only that the risk is variable and may or may not be bimodal." But since clearly the demonstrated increased recurrence risk

for most congenital defects after the occurrence of two affected individuals is not 25%, why not dissect on the basis of trimodality? Having achieved high recurrence risks in one group by lumping unrelated defects, they attempt to bolster the validity of this simple dichotomy by the higher rates of inbreeding in the parents of high-risk than of low-risk cases and indeed, by virtue of the further assumption that the isolated cases with consanguineous parentage really belong with the high-risk group, succeed in eliminating the increased consanguinity rate which the parents of isolated cases exhibit. Since in contrast to others Morton has treated phenodeviants as isolated events in a sibship, this contrived elimination of an inbreeding effect is labeled fatal to the phenodeviant hypothesis.

Phenodeviants, as an expression of multiple homozygosis, should decrease in frequency with outbreeding. The absence of a significant effect of outbreeding on the frequency of congenital malformation in the Hawaii study is thus also taken as evidence against a contribution of phenodeviants to congenital defect. But in fact the (insignificant) effect of major outbreeding on congenital defect is roughly the same as on the other indicators of outbreeding effect. The results of a study on outbreeding will reject the phenodeviant hypothesis when some congenital defects respond differently to outbreeding than known recessively inherited indicators. Otherwise stated, the hypothesis that some meaningful proportion of congenital defects correspond to "phenodeviants" can be challenged when in a set of data phenodeviants can be shown to alter in frequency in a different fashion than a phenomenon due to homozygosity for recessive genes. Where there are no significant outbreeding effects on any indicators, it is impossible to generate a powerful test of hypothesis regarding a specific indicator. Thus, the question must remain *sub judice* until more conclusive data on outbreeding are available. Such studies seem to us to have a higher priority than continued studies of inbreeding effects. A more definitive approach, but one unlikely to succeed for some time because of the many possible genes involved, will be to identify the genes in each phenodeviant system. In any event, in attempts to interpret inbreeding effects, we are once again confronted with the tremendous gap which exists between the mathematical formulations of the theoretist and present difficulties in clean interpretations of data on actual populations.

SUMMARY

An effort has been made to obtain a composite picture of the effects of consanguineous marriage and parental inbreeding in Japan. The end points studied have been morbidity, mortality, frequency of childless marriages, and mean number of children. Fetal loss and death prior to the age of reproduction are both estimated at approximately 4% more in the children of a first-cousin marriage as compared with children resulting from the marriage of unrelated parents. However, because of a lower frequency of childless marriages and a greater mean number of conceptions per marriage, the mean number of surviving conceptions is very similar in the two types of marriage (see table 2).

It is shown that reproductive compensation occurs in consanguineous marriages

in Japan. At the magnitude encountered, it could significantly influence the rate of elimination of recessive genes with lethal effects and estimations of mutation rates for recessive traits.

Calculations based on the concepts of proportional (threshold) selection and an organization and integration of the genes in each chromosome suggest that even these relatively low consanguinity effects are consistent with the maintenance of a large number of polymorphisms through selection. It is emphasized that a calculation of this type must be regarded as illustrative only.

Studies on outbreeding effects should complement those on inbreeding effects. The results of the relatively few recent studies are quite conflicting. It is urged that such studies, where feasible, be pursued vigorously.

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