# Empirical Risks in Consanguineous Marriages: Sex Ratio, Malformation, and Viability[1]

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WITHIN THE LAST DECADE, it has become increasingly apparent that the population genetics of man could and perforce must be explored. The need for information regarding selection, spontaneous mutation rates, etc. in human populations has been most forcefully demonstrated, perhaps, by recent attempts to evaluate the threat to mankind posed by the advent of nuclear energy as a source of power both in peace and in war. While data of a sort exist on the dynamics of human populations, much of the information available is, for one reason or another, unsuited to the needs of the population geneticist. Of late, exploration of certain aspects of human population genetics, notably the consequences of inbreeding, has attracted increasing attention.

The purposes of the present paper are to describe the effects of inbreeding on the sex ratio, the frequency of major congenital malformations, stillbirths, neonatal deaths, and infantile deaths in Japan. The study to be reported is perhaps unique in a number of respects, namely, (1) the prospective orientation of the study, (2) the size of the sample, and (3) the fact that critical observations were, in the main, made by trained observers, usually physicians, and are not dependent upon recall.

## MARRIAGE PRACTICES IN JAPAN

Traditionally, the ideal ages at marriage in Japan are 24 (for boys) and 23 (for girls), and in point of fact, most individuals are either married or negotiating a marriage by 25[2]. There are, of course, a number of considerations, the most important being economic, affecting age at marriage. To some of these considerations we shall return in a moment. But first, we shall address ourselves briefly to three practices common in Japan, namely, (1) the "adoptive son marriage", (2) the affinous marriage, and (3) the consanguineous marriage. The first two of these have an immediate bearing on the frequency of marriages between related persons, and the types of errors which may arise in recording consanguinity in Japan.

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[2] Under the old Civil Code of Japan (effective to 1947), parental consent was required for a son to marry before the age of 30, or a daughter before the age of 25 (Article 772, 1). If marriage occurred without consent, the head of the family could legally expel from the family the offending person or persons (Article 750). At present, parental consent is required only for marriages involving minors (under the age of 21). For details of these provisions of the Civil Codes see Steiner, 1950.

*"Adoptive son marriage":*—Pride in family name is not a characteristic limited to the Japanese, but attempts to ensure the perpetuation of the family name have led to marriage customs in Japan which are uncommon in the United States and Western Europe. In most countries, attempts to perpetuate the family name by means other than through the normal pattern of biologic descent involve the adoption, at a tender age, of a male heir. This practice is, of course, to be found in Japan (the adoptive son is termed a *yōshi*), but an oft-employed alternate is the so-called "adoptive son marriage." Two legal types of such marriage were recognized under the old Civil Code (effective to 1947). These were the *nyūfu* (entering husband) marriage, and the *muko-yōshi* (bridegroom-adoptive son) marriage. The distinction between these types has been clearly drawn by Hozumi (1933). Briefly, it is as follows: In Japan, the headship of a kindred normally passes from eldest son to eldest son. Occasionally the eldest son may be without issue in which case the headship, upon the death of the eldest son, passes through the next oldest son. If the eldest son has only daughters, the eldest daughter is, at least nominally, the head of the kindred. The latter occurrence, however, poses a problem at the time of marriage since normally a wife is enrolled in the *koseki* (household record) of her husband. That is to say, she takes the family name of her husband. In the event that the prospective wife was a household head, the normal convention would create many difficulties. To circumvent these difficulties, two alternatives are available to the female household head. She may select her spouse from among her male relatives having the same family name, in which case the headship does not leave the family. Or, if she selects her spouse from outside her kindred, he may be enrolled in the kindred of his wife. The term *nyūfu* marriage is applied to either of these alternatives, and in neither case does the female relinquish the headship of the kindred. This procedure need not be restricted to female household heads; however, consanguineous marriages are proportionally more frequent among heads of families. Thus, in a small section, Aza Takenoedao, of Shība-mura, Yoshida and Yanase (1951) found that among 32 marriages involving heads of families 56.5 per cent were consanguineous, whereas, among 50 marriages of adult males and 64 marriages of adult females selected without reference to whether the individual was or was not a head of family, 44.0 and 31.3 per cent, respectively, were consanguineous.

In the *muko-yōshi* marriage, the adopted son is married to a daughter, generally the eldest, of the adoptive parent at the time of adoption. This is a legal act which combines marriage and adoption. The headship of the family is then vested in the adopted bridegroom-son.

Neither the *nyūfu* nor the *muko-yōshi* marriage is uncommon as can be seen from Table 1 where the frequencies of these marriages are given for all of Japan as well as selected areas. These types of marriages appear to be on the decline; for example, in 1916, 62.1 in every thousand marriages were a *muko-yōshi* whereas by 1934 this requency had dropped to 51.8.

Our interest in these marriages stems from the fact that the husband is frequently drawn from collateral branches of the family, and consequently the practice of the "adoptive son marriage" tends to enhance the frequency of consanguineous marriages.

TABLE 1. THE FREQUENCY OF "ADOPTIVE SON MARRIAGES" IN JAPAN (DATA DRAWN FROM NIHON TEIKOKU TOKEI NENKAN, 1931; NIHON TEIKOKU JINKO DOTAI TOKEI, 1931, 1934; AND NIHON TEIKOKU JINKO DOTAI TOKEI KIJUTSU-HEN, 1936). SEE TEXT FOR FURTHER EXPLANATION.

| Year | Region | Nyūfu marriage | | Muko-yōshi marriage | | Other marriages | Total marriages |
|---|---|---|---|---|---|---|---|
| 1931 | Nagasaki Prefecture | 191 | 2.1 | 321 | 3.5 | 8,534 | 9,046 |
| | Nagasaki City | 26 | 2.0 | 51 | 3.9 | 1,233 | 1,310 |
| | Hiroshima Prefecture | 362 | 2.5 | 610 | 4.2 | 13,594 | 14,566 |
| | Hiroshima City | 31 | 1.6 | 48 | 2.5 | 1,846 | 1,925 |
| | All Japan | 12,687 | 2.6 | 26,539 | 5.3 | 457,348 | 496,574 |
| 1936 | Nagasaki Prefecture | 201 | 2.1 | 321 | 3.4 | 8,899 | 9,421 |
| | Nagasaki City | 26 | 1.8 | 59 | 4.1 | 1,343 | 1,428 |
| | Hiroshima Prefecture | 297 | 2.0 | 630 | 4.3 | 13,617 | 14,544 |
| | Hiroshima City | 49 | 2.6 | 48 | 2.5 | 1,809 | 1,906 |
| | All Japan | 12,560 | 2.4 | 26,562 | 5.2 | 473,532 | 512,654 |

It would, however, be misleading to leave the impression that all, or even a substantial part of, adoptive son marriages are to ensure perpetuation of the family name. While this is undoubtedly an important factor in the middle and upper economic levels, among members of the lower economic strata, the bulk of whom have had family names only since about 1875, perpetuation of family name is far less important than economic security in motivating adoptive son marriages. In Japan, one's children, and particularly the males, are one's security in old age. Accordingly, parents with only daughters will frequently adopt a son, in one of the manners described, as a buttress against the day when they, the parents, are no longer capable of supporting themselves. While the frequency of this latter event is not known, the consensus of opinion among Japanese interested in marital practices is that it is high.

*Affinous marriages:*—Individuals related by ties of marriage and not blood or descent are said to be affinal relatives, and marriage between two such persons is termed an affinous marriage. Affinous marriages can be of two distinct types based upon whether or not a concomitant of affinity is remarriage. Type A affinous marriages, where remarriage is not a concomitant, would include marriages such as brothers- with sisters-in-law. The genetic extreme of this type of union would be the marriage of identical twins with identical twins. Type B affinous marriages comprise unions of in-law relatives, and involve remarriage of at least one of the partners; these marriages have been classified as first degree when the second marriage involved a brother- or sister-in-law, or second degree, when the second union involved a niece- or nephew-in-law. The levirate marriage, the marriage of a widow to the brother of her deceased spouse, or the sororate marriage, the marriage of a widower to the sister of his deceased spouse, are generally instances of Type B, first degree, affinous marriage; it is not mandatory, however, in the levirate or sororate marriage that wife and husband be unrelated.

The two types of affinous marriages have met with different social barriers in different societies. Neither in Japan nor in Judaeo-Christian societies does there appear to have been an explicit prohibition of the Type A affinous marriage. The situation is somewhat different with respect to the Type B marriage. In Judaeo-Christian societies, these marriages have been banned since the Old Testament wherein there is a specific admonition "Thou shalt not covet thy brother's wife" (Leviticus 18:6–30). No such prohibition or admonition exists for the Japanese.

In-law or affinous marriages are rather frequent occurrences in Japan. Kida et al. (1949), in a survey of marriage practices in Kyushu, report that in-law marriages represent 2.8 per cent of all marriages encountered in their survey. Their data are reproduced in Table 2. Roman Catholic church records in Nagasaki reveal a similar frequency, 2.5 per cent, for the years 1945–1949 (Schull, unpublished data).

Aoyama (1948), in a post war study of remarriage among war widows, has called attention to the frequency of levirate marriages in Japan. Among 92 remarried widows, in 55 cases the second husband was a brother of the deceased spouse; in the remaining 37 cases the second spouse was either unrelated to the first (33 cases) or was a relative other than a sibling (4 cases). Of the 55 marriages involving a brother of the deceased husband, in 52 instances the brother was younger than the deceased husband. The frequency of this event reflects the Japanese view of family responsibilities. Upon the death of an elder, married brother, the burden of support of the widow frequently falls upon one of her unmarried brothers-in-law. The latter individual then faces a dilemma—on the one hand, he must support his brother's wife, and, on the other hand, he desires a wife but generally cannot support two women. A satisfactory solution to this dilemma is obtained if he marries his brother's widow. This convention would tend to maintain a consanguineous union if the deceased brother had selected a relative as a wife, or conversely, to discourage a consanguineous marriage if the deceased brother had selected an unrelated individual as his spouse.

*Consanguineous marriages:*—Though the high frequency of consanguineous marriages in Japan is now a matter of common knowledge, a few words regarding the

TABLE 2. THE FREQUENCY OF AFFINOUS MARRIAGES IN KUMAMOTO PREFECTURE (AFTER KIDA ET AL., 1949)

| Region | Number of couples investigated | Type A affinous marriage | Type B affinous marriage* | Other in-law marriage | Possible in-law marriage** | Total affinous marriages | |
|---|---|---|---|---|---|---|---|
| | | | | | | # | % |
| Kumamoto City | 1,830 | 11 | 3 | 31 | 6 | 45 | 2.5 |
| Yamaga | 2,902 | 22 | 7 | 71 | 3 | 100 | 3.4 |
| Kumafu | 2,908 | 19 | 6 | 54 | 5 | 79 | 2.7 |
| Udo | 1,092 | 4 | 3 | 27 | 2 | 34 | 3.1 |
| Toride | 459 | 2 | 2 | 15 | 0 | 19 | 4.1 |
| Hanabusa | 390 | 5 | 5 | 5 | 0 | 15 | 3.8 |
| Kikuchi | 888 | 9 | 2 | 13 | 1 | 24 | 2.7 |
| Asahino | 416 | 4 | 3 | 8 | 3 | 15 | 3.6 |
| Mizuminato | 776 | 7 | 3 | 9 | 1 | 19 | 2.4 |
| Nagashima (Higashi) | 1,788 | 7 | 0 | 28 | 6 | 35 | 2.0 |
| Nagashima (Nishi) | 1,433 | 5 | 5 | 15 | 14 | 25 | 1.7 |
| Total | 14,882 | 95 | 39 | 276 | 41 | 410 | 2.8 |

* Presumably these figures include only the first two degrees of Type B affinous marriages.
** These uncertain relationships are not included in the totals.

frequency of consanguineous marriages and the attitudes toward these marriages seem essential to an understanding of the data to be presented subsequently.

There is known to the author no nation-wide survey of the proportion of all marriages which are consanguineous in Japan; however, Japanese sociologists and demographers generally assert that some 4–5 per cent of marriages in Japan are between first cousins (see Okazaki, 1941). A brief, and by no means exhaustive, summary of the frequencies of consanguinity thus far reported in 11 of the 46 prefectures of Japan is given in Table 3.

Perhaps the most striking feature of these data is the persistence of high rates of inbreeding in urban centers such as Kumamoto or Tokyo. On the face of the evidence, it would not appear that the association of frequency of consanguineous marriages with size of municipality holds over the range of municipality sizes. For example, the frequencies of first-cousin marriages in Kure (pop. 187,775), Hiroshima (285,712), Nagasaki (241,638), Kumamoto (267,506), and Tokyo (5,385,071) differ only by a factor of two despite the fact that population size, in 1950, varies by as much as thirty-fold. There is much cultural evidence to suggest, however, that the larger cities are merely aggregations of villages. The rates of consanguinity in urban centers would support this general notion since the frequency of consanguineous marriages seems to plateau once a certain city size is attained. One cannot approach this argument with much rigor, however, since many of the marriages encountered in urban areas will have been contracted before migration to the city, or arranged after migration with someone from the village of origin. The "true" incidence of consanguineous marriage within urban "isolates" in Japan is unknown.

Considerable effort on the part of Japanese investigators has been expended on the studies of the so-called "consanguinity villages" to be found scattered throughout Japan. Among such villages which have been studied are Narata (Nishiyama-mura, Yamanashi Prefecture; Shinozaki, 1955), Gokanosho (Kumamoto Prefecture; Kida et al., 1949; Kanokogi, 1952; Kanokogi and Kaku, 1952), Shība (Miyazaki Prefecture; Yanase, 1949, 1951), Ōaza Tsuru (Umibe-mura, Oita Prefecture; Ikemi, 1936), and Aza Maruyama (Shinmaru-mura, Ishikawa Prefecture; Maruyama et al., 1935). The origins of these mountain villages, insofar as they are known, read like footnotes to Japanese history. Narata, for example, is said to have been founded in the Nara Era during the reign of the Empress Koken (about 1200 years ago). Legend has it that the Empress had fallen ill, and, in a fever-racked dream, saw a hot spring with curative powers located in the northern part of the country. Immediately she dispatched some of her retainers to search for this miraculous spring. The spring, which these men found and were charged to guard in perpetuity, as it were, is now called Nishiyama onsen. The present villagers are alleged to be the descendants of the guardsmen and their families who because of their isolation intermarried generation after generation. Needless to say, it has not been possible to authenticate this charming legend although a fairly reliable village history extending back some 400 years does exist. That the legend may not be entirely the figment of some vivid imagination is suggested by the language of the villagers, *narata kotoba*, which differs substantially from the language spoken in adjacent areas, the earthenware produced in the village, which is like that produced in the Nara Era, and the structure of the

TABLE 3. THE FREQUENCY OF CONSANGUINEOUS MARRIAGES IN VARIOUS PARTS OF JAPAN

| Prefecture | Village or Town | Number of couples Investigated | Consanguineous marriages | | First cousin marriages | | 1½ Cousin | | Second Cousin | | Investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | # | % | # | % | # | % | # | % | |
| Fukushima | Okisawa | 483 | 59 | 12.2 | 38 | 7.9 | 9 | 1.9 | 12 | 2.5 | Ichiba, 1953 |
| | Koizumi | 173 | 18 | 10.4 | 15 | 8.7 | 1 | 0.6 | 2 | 1.2 | " " |
| Nagano | Ono | 624 | 131 | 21.0 | 81 | 13.0 | 16 | 2.6 | 34 | 5.5 | Kubota et al., |
| | Kawajima | 414 | 117 | 28.3 | 68 | 16.4 | 15 | 3.6 | 34 | 8.2 | 1950 |
| | Tatsuno | 2,195 | 279 | 12.7 | 172 | 7.8 | 24 | 1.1 | 83 | 3.8 | " " |
| | Asahi | 1,148 | 160 | 13.9 | 99 | 8.6 | 19 | 1.7 | 42 | 3.7 | " " |
| | Nakaminowa | 2,551 | 380 | 14.9 | 235 | 9.2 | 33 | 1.3 | 112 | 4.4 | " " |
| | Higashi Minowa | 625 | 110 | 17.6 | 61 | 9.8 | 17 | 2.7 | 32 | 5.1 | " " |
| | Minowa | 506 | 66 | 13.0 | 47 | 9.3 | 4 | 0.8 | 15 | 3.0 | " " |
| | Fujisawa | 663 | 159 | 24.0 | 95 | 14.3 | 14 | 2.1 | 50 | 7.5 | " " |
| | Nishi Minowa | 1,069 | 208 | 19.5 | 134 | 12.5 | 28 | 2.6 | 46 | 4.3 | " " |
| | Minami Minowa | 891 | 127 | 14.3 | 83 | 9.3 | 13 | 1.5 | 31 | 3.5 | " " |
| | Tera | 726 | 123 | 16.9 | 83 | 11.4 | 13 | 1.8 | 27 | 3.7 | " " |
| | Nagafuji | 420 | 75 | 17.9 | 47 | 11.2 | 9 | 2.1 | 19 | 4.5 | " " |
| | Miyoshi | 400 | 107 | 26.8 | 56 | 14.0 | 10 | 2.5 | 41 | 10.3 | " " |
| | Miwa | 727 | 147 | 20.2 | 68 | 9.4 | 10 | 1.4 | 69 | 9.5 | " " |
| | Nagato | 662 | 63 | 9.5 | 44 | 6.6 | 8 | 1.2 | 11 | 1.7 | " " |
| | Inacho | 3,353 | 381 | 11.4 | 238 | 7.1 | 45 | 1.3 | 98 | 2.9 | " " |
| | Nishi Haruchika | 1,029 | 159 | 15.5 | 97 | 9.4 | 26 | 2.5 | 36 | 3.5 | " " |
| | Midori | 734 | 143 | 19.5 | 86 | 11.7 | 15 | 2.0 | 42 | 5.7 | " " |
| | Tomigata | 990 | 169 | 17.1 | 100 | 10.1 | 20 | 2.0 | 49 | 4.9 | " " |
| | Kanname | 476 | 80 | 16.8 | 57 | 12.0 | 5 | 1.1 | 18 | 3.8 | " " |
| | Miyata | 760 | 129 | 17.0 | 81 | 10.7 | 15 | 2.0 | 33 | 4.3 | " " |
| | Higashi Haruchika | 732 | 154 | 21.0 | 94 | 12.8 | 15 | 2.1 | 45 | 6.1 | " " |
| | Ina Mura | 372 | 80 | 21.5 | 55 | 14.8 | 10 | 2.7 | 15 | 4.0 | " " |
| | Inasato | 417 | 89 | 21.3 | 54 | 12.9 | 10 | 2.4 | 25 | 6.0 | " " |
| | Nakazawa | 1,312 | 216 | 16.5 | 146 | 11.1 | 24 | 1.8 | 46 | 3.5 | " " |
| | Nomukai | 797 | 135 | 16.9 | 89 | 11.2 | 17 | 2.1 | 29 | 3.6 | " " |
| | Akaho | 3,195 | 424 | 13.3 | 283 | 8.9 | 44 | 1.4 | 97 | 3.0 | " " |
| | Kamikatagiri | 624 | 74 | 11.9 | 45 | 7.2 | 9 | 1.4 | 20 | 3.2 | " " |
| | Iijimi | 1,327 | 178 | 13.4 | 118 | 8.9 | 16 | 1.2 | 44 | 3.3 | " " |
| | Nanakubo | 601 | 105 | 17.5 | 63 | 10.5 | 11 | 1.8 | 31 | 5.2 | " " |
| | Katagiri | 644 | 123 | 19.1 | 83 | 12.9 | 16 | 2.5 | 24 | 3.7 | " " |
| | Nakata machi | 805 | 57 | 7.1 | 48 | 6.0 | 2 | 0.2 | 7 | 0.9 | Kishimoto, 1954 |
| Aomori | Narusawa | 335 | 9 | 2.7 | 8 | 2.4 | 1 | 0.3 | 0 | 0 | Ichiba, 1953 |
| Chiba | Tsuchi | 1,314 | 17 | 1.3 | 10 | 0.8 | 1 | 0.1 | 6 | 0.5 | " " |
| Fukuoka | Shigazima-mura | 349 | 59 | 16.9 | 33 | 9.5 | 5 | 1.4 | 15 | 4.3 | Yanase, 1951 |
| Gifu | Tokuyama-mura | 49 | 15 | 30.6 | 13 | 26.5 | 0 | 0 | 2 | 4.1 | Kishimoto, 1954 |
| | Takane-mura | 101 | 5 | 5.0 | 5 | 5.0 | 0 | 0 | 0 | 0 | " " |
| | Itadori | 993 | 131 | 13.2 | 102 | 10.3 | 6 | 0.6 | 23 | 2.3 | Ichiba, 1953 |
| | Shimomaki | 1,007 | 62 | 6.2 | 46 | 4.6 | 5 | 0.5 | 11 | 1.1 | " " |
| | Kaminoko | 682 | 38 | 5.6 | 34 | 5.0 | 1 | 0.1 | 3 | 0.4 | " " |
| | Tominoko | 412 | 59 | 14.3 | 50 | 12.1 | 3 | 0.7 | 6 | 1.5 | " " |
| | Nakayūchi | 616 | 59 | 9.6 | 44 | 7.1 | 7 | 1.1 | 8 | 1.3 | " " |
| Kumamoto | Kumamoto | 1,830 | 117 | 6.4 | 63 | 3.4 | 31 | 1.7 | 23 | 1.3 | Kida et al., 1949 |
| | Yamaga | 2,902 | 250 | 8.6 | 162 | 5.6 | 42 | 1.4 | 46 | 1.6 | " " |
| | Kumafu | 2,908 | 275 | 9.5 | 175 | 6.0 | 48 | 1.7 | 52 | 1.8 | " " |

TABLE 3—*Concluded*

| Prefecture | Village or Town | Number of couples Investigated | Consanguineous marriages | | First cousin marriages | | 1½ Cousin | | Second Cousin | | Investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | # | % | # | % | # | % | # | % | |
| Kumamoto | Udo | 1,092 | 97 | 8.9 | 56 | 5.1 | 15 | 1.4 | 26 | 2.4 | Kida et al., 1949 |
| | Toride | 459 | 64 | 13.9 | 39 | 8.5 | 13 | 2.8 | 12 | 2.6 | " " |
| | Hanabusa | 390 | 49 | 12.6 | 33 | 8.5 | 6 | 1.5 | 10 | 2.6 | " " |
| | Kikuchi | 888 | 124 | 14.0 | 84 | 9.5 | 14 | 1.6 | 26 | 2.9 | " " |
| | Asahino | 416 | 55 | 13.2 | 28 | 6.7 | 15 | 3.6 | 12 | 2.9 | " " |
| | Suigen | 776 | 140 | 18.0 | 96 | 12.4 | 29 | 3.7 | 15 | 1.9 | " " |
| | Higashi Nagashima | 1,788 | 306 | 17.1 | 204 | 11.4 | 45 | 2.5 | 57 | 3.2 | " " |
| | Nishi Nagashima | 1,433 | 298 | 20.8 | 205 | 14.3 | 38 | 2.7 | 55 | 3.8 | " " |
| Hiroshima | Kure | 8,211 | 575 | 7.0 | 320 | 3.9 | 115 | 1.4 | 140 | 1.7 | This paper |
| | Hiroshima | 27,934 | 1,653 | 5.9 | 944 | 3.4 | 317 | 1.1 | 392 | 1.4 | " " |
| Nagasaki | Nagasaki | 33,319 | 2,667 | 8.0 | 1602 | 4.8 | 414 | 1.2 | 651 | 2.0 | " " |
| Aichi | Sakushima-mura | 437 | 30 | 6.9 | 26 | 6.0 | 3 | 0.7 | 1 | 0.2 | Kishimoto, 1954 |
| | Nagoya | 9,569 | 251 | 2.6 | 205 | 2.1 | 10 | 0.1 | 36 | 0.4 | " " |
| Kagawa | Fukuda-mura | 629 | 19 | 3.0 | 19 | 3.0 | 0 | 0 | 0 | 0 | " " |

homes, which bears little similarity to that commonly found in rural areas and is more reminiscent of the architecture employed, in the feudal period, in fashioning the homes of the nobility. Be this as it may, of some 28 marriages occurring in this village since 1944, 10 involved first cousins, 5 second cousins, and in the remainder the individuals were more remotely related. More striking, however, are Kida's findings in Gokanosho, an isolated mountain village of over 7000 inhabitants. Here over 40 per cent of the marriages are consanguineous.

Undoubtedly a variety of factors are operating to maintain the high frequency of related marriages in Japan, but certainly two of the more important are the custom of arranged marriages (*baishaku kekkon*) and the family system. The custom and prevalence of arranged marriages is succinctly stated in *Japan: The Official Guide*, a governmental publication, as follows: "Although there are some love marriages and of late years these have been increasingly numerous, most marriages are arranged by friends of the families who act as go-betweens of each party after careful inquiries have been made as to the suitability of the proposed match. There still exists an idea in Japan that marriage is the beginning of love and not the end of it." A number of considerations enter into the arranging of a marriage. Firstly, until such time as a younger son can afford to establish a branch household, or, in the case of an eldest son, until the parents die, the newly married couple will reside with the husband's family. To maintain a home in peace it is essential, then, to select a bride of known disposition, born and reared in an environment relatively similar to that of the groom's family. Secondly, the economic status of each family is of importance. It is generally considered best to arrange a marriage with the families on about equal economic level, or with the girl's family slightly poorer. If there is a marked discrepancy in economic status, with the boy's family the poorer, the bride's family will feel obliged to give their daughter and son-in-law some financial support either directly or indirectly; whereas if the bride's family is markedly poorer, since various

TABLE 4. A SUMMARY OF SOME OF THE REASONS ADVANCED FOR CONSANGUINEOUS MARRIAGES (AFTER ICHIBA, 1953)

| Reason | Number |
|---|---|
| Geographic reasons | 40 |
| To settle economic problems | 40 |
| Problems of inheritance | 4 |
| Prospective mates know each other well | 150 |
| He (or she) is the only possible mate | 22 |
| No complications involved in arranging a marriage | 6 |
| Childhood betrothals | 14 |
| Simply repeated the precedent established by parents | 8 |
| Requested by will | 10 |
| A desire to expand the circle of relatives | 34 |
| To maintain peace in the family | 8 |
| Other | 13 |
| Total | 349 |

gifts are expected at the birth of a child, etc., the bride's family will feel obliged to make an onerous effort to give impressive gifts. In either case, an undue economic hardship is worked on one of the families, and, of course, the other family loses "face." Given these considerations, relatives may become ideal matches.

A further illustration of the value of consanguineous marriage in meeting problems posed by the family system arises in connection with family property. It is customary in Japan, particularly in the rural areas, for family holdings to be used collaboratively by the sons and daughters so long as their father survives. Upon his death, the property is divided among his children and grandchildren, the custom of *sandai no bunkatsu*, the third generation partition. In the past, the eldest son received the lion's share of the family holdings, and the portions received by the other individuals were frequently inadequate to support a family. One effective means of restoring the property to something approaching its former size was for the grandchildren to marry one another.

Some notion of the reasons motivating persons to marry relatives can be obtained from data collected by Ichiba (1953) in the villages of Itadori, Ina, Katagiri, and Okizawa. Each of 349 couples who were related were requested to indicate the principal reason, in their opinion, for related marriages. The results of this inquiry are given in Table 4.[3] It should be noted that the most common reasons advanced for related marriages are geographic, to settle economic problems, and "prospective mates know each other well." We have already commented on the importance, in Japanese eyes, of knowing the graces and foibles of one's mate prior to marriage, and on economic factors favoring consanguineous marriages. The remaining commonly advanced explanation, geographic reasons, does not necessarily imply geographic proximity. In some areas of Japan, *buraku* (hamlet) exogamy is the rule in arranging marriages. Frequently when a young man's marriage is to be arranged in a

[3] Ichiba appears to assume that the answers volunteered by these individuals reflect the motivations in their own marriages. Whether or not this is true is debatable. Responses in circumstances such as this often reflect what is considered culturally desirable rather than individual opinions.

village practicing exogamy, the family is largely compelled to select his mate from relatives since they alone, of the persons living outside the village, would be adequately known to the prospective groom's family.

Let us turn now to a consideration of the attitudes toward consanguineous matches. The official attitude, as revealed by the recent Civil Codes of Japan, is one of forbidding the marriage of relatives of certain specified degrees (under the old code effective until 1947, Article 769; under the present code, Article 734). Thus, the old code, for example, states that "relatives of the direct line, or the collateral relatives within the third degree (aunt-nephew; uncle-niece) cannot marry. But marriage between a *yōshi* and a collateral relative of the adoptive father is excepted." As Nakagawa (1953) has pointed out, this law follows the spirit of similar laws in a number of European countries (e.g., Article 1310, German Civil Code; Article 100, Swiss Civil Code). Interestingly, however, the Japanese code does not specify a penalty associated with the violation of this law, and apparently no effort is made to enforce this article. In Japan, a civil marriage ceremony is not required. One is, however, required to register the fact of marriage with the municipal authorities. At this registration no serious attempt is generally made to ascertain relationship between husband and wife.

The present official attitude is not of recent origin. The Code of a Hundred Articles (*O-Sadame-gaki Hyakkajō*), attributed to Ieyasu Tokugawa but probably written sometime in the 18th Century, observes "One should not live alone after 16 years of age, but should procure a mediator, and perform the ceremony of matrimonial alliance. The same kindred, however, may not intermarry." (Art. XLVI, see Murdoch, 1926, Vol. III, p. 803). An even earlier code, the *Buke-Hatto* (Laws of the Military Houses) promulgated in 1615, asserts "Marriages must not be contracted at private convenience." These laws were directed largely toward the feudal nobility, but even here, they were frequently violated as is apparent on perusal of the *Kansei Chōshū Shō Kafu* (Official Collection of the Genealogies of the *Daimyo*). There is little evidence that these prohibitions were followed by the farmers and artisans.

Among the religious groups in Japan, only the Christian ones place a prohibition on consanguineous marriages (see Schull, 1953). We have been unable to find any restrictions with respect to relationship placed upon marriage by either the Buddhist or Shinto religions. Marriage of relatives is not, however, encouraged by the priests of either religion.

The attitude of the Japanese, in general, toward consanguineous unions has been simply stated in the Japanese Folklore Dictionary (*Minzoku-Jiten*, 1951) as "cousin marriages are even considered desirable." There is, however, a growing awareness of the biologic risks associated with the marriage of relatives. This awareness has been fostered of late by an increasing number of popular articles pointing out the risks (Taniguchi, 1951; Y. Tanaka, 1952; K. Tanaka, 1955). At the same time, there is a continuing tendency to view such marriages as an admissible solution to a variety of problems stemming from the family system prevailing in Japan. Attempts to resolve these two points of view have led to a number of interesting permutations of marriage practices. Thus, for example, it is commonly held by the less educated Japanese that the father of a child is, in some inexplicable fashion, the more important determiner of the attributes of the child. And from this premise the conclusion is drawn that the risk involved in the marriage of offspring of sisters should be less than in the offspring of brothers. The marriage of the offspring of sisters would, then, more adequately serve the two points of view given above than would the marriage of the offspring of brothers. In a traditionally male-oriented society, such as the Japanese, the initial premise on which this line of reasoning is based is, perhaps, not unexpected. That this common belief may find expression in the choice of a mate seems indicated by data reported by Yanase (1951) and Morton (1955). In a study of the randomness of the four types of first-cousin marriages in Hiroshima, Nagasaki, and Kure in 1948–1952, Morton observed the following in 689 first cousin marriages: 149 involved the offspring of brothers, 229 involved the offspring of sisters, and 311 involved the offspring of a brother and a sister (in 127 cases marriage involved brother's son with sister's daughter). The greatest departure from expectation under an hypothesis of a random distribution of the types of first-cousin marriages is, it will be noted, the increased frequency of the marriage of the offspring of sisters. Whether these figures are typical of Japan is not clear. Embree (1939), on the basis of a study of Suye-mura in Kyushu has asserted that the most common marriage among first cousins involves the offspring of brothers; whereas Beardsley, Hall, and Ward (1958) observed that brother's son with sister's daughter marriages were the most common. These seemingly contradictory results would be reconcilable if the pattern of first-cousin marriages is different among the heads of families from that obtaining among individuals who will establish branch households. In urban areas, branch households would doubtless be relatively more frequent than in rural areas since the founders of branch households are more free to migrate, not being restricted by traditional land holdings.

## THE DATA

The circumstances leading to the collection of these data as well as the method by which they were collected have been described *in extenso* elsewhere (Neel and Schull, 1956). Briefly, the data were collected as one facet of a comprehensive attempt to obtain detailed information concerning the various possible late or delayed biological effects of exposure to an atomic bombing. More precisely, the data to be reported arose as a by-product of an attempt to determine whether there can be observed, during the first year of life, any difference between the children born to parents, one or both of whom were exposed to the effects of the atomic bombings of Hiroshima and Nagasaki, and the children born to selected 'control' parents. Since the details of the data collection have been described elsewhere, we shall merely outline the process here, adding certain additional information bearing on the ascertainment of consanguinity.

Prevailing in Japan during the course of this study was a ration system such that pregnant women upon registration of their pregnancy following the completion of the fifth month of gestation could obtain access to certain rationed items. With the assistance of the city administrators of Hiroshima, Nagasaki, and Kure, a system was instituted whereby, at the time of her registration for ration purposes, each pregnant woman or her representative completed the first two-thirds of a questionnaire which included such items as identifying information, consanguinity, a short summary of the past reproductive performance, and pertinent details concerning the present pregnancy. This questionnaire, which was administered by trained clerks, was filled out in duplicate; the original was given the registrant, while the Atomic Bomb Casualty Commission, the agency charged with ascertaining the delayed effects of the atomic bombing, retained the copy. At the termination of the pregnancy, the midwife or physician in attendance completed the questionnaire by answering certain questions pertaining to the characteristics of the child and delivery, and notified the Commission of the termination of the pregnancy. Irrespective of the outcome of the pregnancy, a Japanese physician in the employ of the Commission or the Japanese National Institute of Health called to examine the child. Through the attendant at birth and/or the examining physician, information was obtained on the sex, birthweight, and presence of malformation in the child as well as whether the child was live or stillborn, and if liveborn, whether death occurred in the first month of life. The Commission's physician in addition to examining the child verified certain items of information obtained at the time of registration. While the bulk of these items had to do with identification of the pregnancy, included among them was the occurrence of consanguinity.

If upon examination the child was found to be abnormal, in the sense that the child possessed a major congenital malformation, was stillborn, or died during the neonatal period, a more-detailed questionnaire was completed by the examining physician. While the primary purpose of this questionnaire was to obtain more-detailed information on the abnormality, information was also collected with respect to the occurrence of defect in the mother's or father's family, gynecologic history, maternal disease during pregnancy, past reproductive performance, and economic status. In addition, blood was drawn from the mother for a serologic test for the presence of syphilis. This same procedure was followed routinely on every pregnancy where the registration number, assigned in sequence at the time of registration, terminated in zero.

Two additional sources of data require brief mention here. Firstly, a concerted attempt was made, particularly in Hiroshima, to obtain for necropsy the bodies of infants who were stillborn or died in the first seven days of life. In Hiroshima and Nagasaki combined, 89 infants born to related parents came to necropsy; of this number, 60 were the offspring of registered parents. Secondly, in 1950, there was inaugurated a program to reexamine, at the age of 9 months, the children examined shortly after birth. The number of these reexaminations was determined by the available clinical facilities. To obtain a sample, selection of the infants to be seen was by the terminal registration digit of the pregnancy. In the event that it was not possible to examine a child, who was included in the sample, an effort was made to establish why, in an attempt to detect possible sources of bias. Of the total infants selected for examination, in about five per cent of cases the parents had moved from the city some time after the birth of the infant selected, and in slightly less than one per cent of cases the child was not seen for a variety of other reasons, including the refusal of the parents to have the child examined, and illness in the family at the time of the scheduled clinic visit. There is no indication in these data that failures to examine children selected for study were more frequent when the parents were unrelated than when they were related. The purposes of this second examination were several-fold. It afforded a check on diagnostic oversights at the first examination and an opportunity for supplemental diagnoses. It permitted extension of the distribution of infant deaths from one week to 9 months of age. Finally, it presented an occasion to appraise the mental and physical growth and development of these children not otherwise possible.

In addition to the verification of consanguinity by the examining physician to which we have previously alluded, verification was routine whenever the mother registered for a subsequent pregnancy (approximately one-fourth of the mothers registered more than once during the course of the study). In the event of a discrepancy in responses, a further attempt to verify the information was made by sending a trained interviewer to interview the mother. In a sample of more than 6000 consecutive registrations, 16 corrections of consanguinity information were made by the examining physician, and 14 through verification of a previous registration; among the latter, in six instances the verified information differed from both registrations. Collectively, there were 15 instances of consanguinity not ascertained at registration, and 14 changes in degree of consanguinity. No instance of denial of previously reported consanguinity was recorded. In general, an effort was made to uncover all relationships up to and including second cousins. If the individuals knew of more remote relationship, this was recorded; however, no special attempt was made to probe for distant relationships. It must be clearly recognized, therefore, that there exists within these data some unrecognized inbreeding (we shall indicate later the probable magnitude of this covert inbreeding), and that "unrelated" parents are merely individuals reporting themselves to be unrelated. We may safely assume that if some of the latter individuals are, in fact, related, it is unlikely that they are more closely related than second cousins.

To determine more accurately the reliability of the consanguinity information, Japanese physicians in the employ of the ABCC carefully verified 768 registrations by revisiting the mother. The sample chosen for verification consisted of parents reported to be first cousins, first cousins once removed, or second cousins, whose registration numbers ended in 1 or 6. The sample was so chosen for two reasons. Firstly, since corrections of degree of relationship were almost as frequent as corrections in fact of consanguinity, despite the fact that consanguinity occurs in less than 10 per cent of the marriages here recorded, it seemed clear that determination of degree of consanguinity was the weakest part of the data. Secondly, it was the impression of the various interviewers that Japanese parents were well informed of consanguinity between husband and wife and not indisposed to discuss their relationship, but that degree of consanguinity was sometimes poorly ascertained by the interviewer. The results of this special verification study are presented in Table 5. It will be noted that the consanguinity information is not without error despite the several checks to which it was subjected. One common source of error was the failure to record the details of multiple relationships or relationship through a single common ancestor

TABLE 5. RELIABILITY OF THE CONSANGUINITY DATA AS JUDGED BY SPECIAL VERIFICATION OF A SAMPLE OF REPORTEDLY RELATED PARENTS

| Previous record of parental relationship | Verified record of parental relationship | | | | | | | F | |
|---|---|---|---|---|---|---|---|---|---|
| | First cousins | 1½ cousins | Second cousins | Remote, degree uncertain | Not related | Other | Total | Obs. | Exp. |
| First cousins | 433 | 3 | 7 | 1 | 4 | 15 | 463 | .0604 | .0625 |
| 1½ cousins | 1 | 95 | 6 | — | 2 | 6 | 110 | .0311 | .0313 |
| Second cousins | 4 | 14 | 155 | 5 | 4 | 13 | 195 | .0171 | .0156 |
| Total | 438 | 112 | 168 | 6 | 10 | 34 | 768 | | |

(half cousins, etc.). Ten of the parents were not related by blood; of these, 2 were related by adoption, 3 by marriage, 3 by a previous marriage, for 1 case no details were given, and in 1 case there was an error in coding. In the entire sample, 683 cases appear to have been correctly ascertained, and among the remainder, the errors are distributed such that the "observed" inbreeding coefficient is, for each degree of relationship, nearly identical with its theoretical value. Because of this cancellation of errors, the consanguinity data are considerably more reliable than might be supposed from the frequency of corrections alone, and random errors can probably be neglected. The author is unaware of any other consanguinity study in which an attempt has been made to determine the reliability of responses in a manner similar to that here presented. It is not possible, therefore, to form an opinion as to whether the errors in ascertaining consanguinity in Japan are greater or less than usual.

We shall in the ensuing sections restrict our attentions to those registered pregnancy terminations where neither parent sustained exposures to nuclear energy exceeding class 2 (estimated mean dose 5 reps; see Neel and Schull, 1956). By so restricting the data there is little possibility of confounding radiation and inbreeding effects. In this connection, it is perhaps worth pointing out that in some 60 per cent of the cases to follow neither parent was exposed.

In addition to the rejection of certain pregnancy terminations on the basis of parental exposure to the atomic bombings, a pregnancy termination was rejected if (1) the termination was induced and the birth weight of the infant was less than 2,500 grams, (2) the birth weight was not recorded, (3) the birth rank (parity) was not recorded, (4) the gestation was less than 21 weeks, or unknown and the infant weighed less than 2,500 grams, (5) the sex of the infant was not recorded, or (6) the age of the mother was unknown. A justification of these various bases for rejection is to be found in Neel and Schull (1956). Two differences between the present study and that of Neel and Schull in cases which were rejected are the inclusion, here, of diagnoses of congenital heart disease, and the infants seen at nine months of age on whom an incomplete set of anthropometric measurements was obtained.

## THE COMPARABILITY OF THE SUBCLASSES OF RELATIONSHIP

In this section as well as in the sections to follow, in considering relationship, we shall restrict ourselves to four groups, namely, unrelated parents, first cousins, first cousins once removed (1½ cousins), and second cousins. A few uncle-niece and some unions of more remote relationship than second cousins were enumerated. These two groups have been excluded for two reasons. Firstly, the numbers are too small to analyze with much profit, and secondly, it is certain that relationships more remote than second cousins were not exhaustively ascertained.

As has been indicated, the data are drawn from three cities, Kure, Hiroshima and Nagasaki. A brief description of the nature of Hiroshima and Nagasaki will be found in Neel and Schull (1956). Kure is a city of rather recent origin stemming primarily from the establishment of the Kure Naval Yards in June, 1889. As these yards grew—by 1940 they were the largest naval yards in Japan—they dominated the economic life of the city. Until the end of World War II, the development of Kure was largely determined by what best served the interests of the Japanese Navy. In the post-war period, Kure has been a major center of the forces occupying Japan. Thus, at no time in its existence has Kure been a "typical" Japanese city. The data collected in Kure were obtained in the years 1948–1950 when it was uncertain whether Hiroshima would rebuild rapidly enough to provide an adequate internal control for the radiation studies. As soon as it became apparent that an adequate control could be obtained in Hiroshima, the studies in Kure were terminated.

These three cities and the subclasses of relationship differ in a number of important respects to which we now turn our attention. Table 6 presents the distribution of the

TABLE 6. THE DISTRIBUTION OF PARENTAL RELATIONSHIPS AMONG REGISTERED INFANTS BORN IN HIROSHIMA, KURE, AND NAGASAKI IN THE YEARS 1948–1954

| City | Parental relationship | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | Unrelated | First Cousins | | 1½ Cousins | | Second Cousins | | |
| | n | n | p | n | p | n | p | |
| Hiroshima: | | | | | | | | |
| 1948 | 2,704 | 117 | .0402 | 40 | .0137 | 50 | .0172 | 2,911 |
| 1949 | 5,959 | 208 | .0329 | 65 | .0103 | 91 | .0144 | 6,323 |
| 1950 | 5,153 | 220 | .0399 | 75 | .0136 | 67 | .0121 | 5,515 |
| 1951 | 4,604 | 178 | .0362 | 53 | .0108 | 83 | .0169 | 4,918 |
| 1952 | 4,088 | 125 | .0290 | 41 | .0095 | 52 | .0121 | 4,306 |
| 1953 | 3,744 | 93 | .0237 | 43 | .0109 | 49 | .0125 | 3,929 |
| 1954 | 29 | 3 | | — | | — | | 32 |
| Total | 26,281 | 944 | .0338 | 317 | .0113 | 392 | .0140 | 27,934 |
| Kure: | | | | | | | | |
| 1948 | 1,626 | 84 | .0473 | 27 | .0152 | 39 | .0220 | 1,776 |
| 1949 | 4,175 | 141 | .0317 | 65 | .0146 | 71 | .0159 | 4,452 |
| 1950 | 1,835 | 95 | .0479 | 23 | .0116 | 30 | .0151 | 1,983 |
| Total | 7,636 | 320 | .0390 | 115 | .0140 | 140 | .0171 | 8,211 |
| Nagasaki: | | | | | | | | |
| 1948 | 648 | 38 | .0534 | 10 | .0140 | 16 | .0225 | 712 |
| 1949 | 7,385 | 422 | .0523 | 95 | .0118 | 163 | .0202 | 8,065 |
| 1950 | 6,410 | 353 | .0504 | 91 | .0130 | 149 | .0213 | 7,003 |
| 1951 | 6,008 | 300 | .0461 | 81 | .0125 | 116 | .0178 | 6,505 |
| 1952 | 5,580 | 292 | .0481 | 79 | .0130 | 117 | .0193 | 6,068 |
| 1953 | 4,573 | 197 | .0401 | 57 | .0116 | 90 | .0183 | 4,917 |
| 1954 | 48 | — | | 1 | | — | | 49 |
| Total | 30,652 | 1,602 | .0481 | 414 | .0124 | 651 | .0195 | 33,319 |
| Total | 64,569 | 2,866 | .0413 | 846 | .0122 | 1,183 | .0170 | 69,464 |

four classes of relationship by city and year of registration of the infant. In all three cities, the initial and terminal years recorded are incomplete due to either the initiation or termination of observations at some date other than January 1. The frequencies of consanguineous marriages in these data lead to average coefficients of inbreeding ($\alpha$) of 0.00269 (Hiroshima), 0.00314 (Kure), and 0.00370 (Nagasaki). Since consanguineous marriages in Japan have undoubtedly been more common in the past, and since these coefficients are computed on the assumption that the common ancestors were themselves not inbred, these values unquestionably underestimate the true coefficients of inbreeding. It is difficult to determine to what extent these are underestimates; however, from data collected by Nagashima (1949) on red-green colorblindness on the island Sado (in the Japan Sea near the city of Niigata), one can estimate that the true inbreeding coefficients may be as much as one-third higher. To arrive at this correction requires, of course, certain assumptions regarding the frequency with which heterozygous females exhibit red-green colorblindness, and randomness of cousin matings.

Inspection of Table 6 reveals several items of interest. Firstly, Hiroshima and Nagasaki clearly exhibit temporal trends, the proportion of births to related parents diminishing with time. Secondly, "total" consanguinity, here defined as the proportion of all infants born to parents related as first cousins, first cousins once removed, or second cousins, differs significantly between cities ($\chi^2$ = 101.058, DF = 2). Lastly, the proportion of first cousin marriages among all related marriages differs between cities, not significantly but nearly so ($\chi^2$ = 5.936, DF = 2). The totals in subsequent tables will differ somewhat from those in Table 6 due to the exclusion of multiple births. In this connection, it can be shown that the frequency of multiple births does not differ significantly nor appreciably among the classes of relationship.

There exist reasons for suspecting that individuals who contract marriages with relatives may differ with respect to a number of socio-economic factors from those individuals who are unrelated to their spouses. Available to test this thesis are data on maternal age at the termination of the registered pregnancy, number of conceptions of a given mother, the economic status of the parents, the frequency of positive serology among parturient mothers, and the age differential between husband and wife. There follows a brief consideration of the distributions of these socio-economic concomitants of marriage among the classes of parental relationship.

In Tables 7 and 8 are presented data on economic status and frequency of positive serological tests for syphilis among parturient mothers by city and parental relationship. In any appraisal of the data with regard to economic status, the following should be borne in mind: The determination of economic status was a value judgment by a physician in the employ of ABCC or the Japanese National Institute of Health made at the time of the home visit examination of the child. Each family was assigned to one of five economic classes, namely, very poor, poor, average, well-to-do, and rich. The roughness of this scheme is apparent; however, since in the course of time each physician found himself in all sections of a city, among all economic classes, and among all classes of parental relationship, it seems likely that even this rough classification would detect any marked difference among related classes within a city. The subjectivity of the classification makes it difficult, however, to evaluate the reality

TABLE 7. THE DISTRIBUTION OF ECONOMIC STATUSES BY CITY AND PARENTAL RELATIONSHIP

| City | Economic status | Parental relationship | | | |
|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated |
| Hiroshima | Below | 32 | 12 | 17 | 751 |
| | Average | 317 | 115 | 134 | 6,917 |
| | Above | 12 | 3 | 5 | 435 |
| Kure | Below | 5 | 1 | 3 | 162 |
| | Average | 66 | 26 | 36 | 1,525 |
| | Above | 5 | 1 | 1 | 108 |
| Nagasaki | Below | 54 | 17 | 24 | 1,175 |
| | Average | 284 | 68 | 114 | 5,315 |
| | Above | 17 | 4 | 10 | 342 |

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Hiroshima | 7.054 | 6 | .25–.50 |
| Kure | 3.298 | 6 | .75–.90 |
| Nagasaki | 2.251 | 6 | .75–.90 |

TABLE 8. THE DISTRIBUTION OF POSITIVE SEROLOGICAL TESTS FOR SYPHILIS BY CITY AND RELATIONSHIP OF MOTHER TO HER SPOUSE. THE NUMBER OF MOTHERS WITH POSITIVE SEROLOGICAL TESTS FOR SYPHILIS IS INDICATED BY +

| City | | Parental Relationship | | | | Total |
|---|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated | |
| Hiroshima | n | 350 | 126 | 152 | 7,659 | 8,287 |
| | + | 12 | 4 | 2 | 278 | 296 |
| | p | .0343 | .0317 | .0132 | .0363 | .0357 |
| Kure | n | 67 | 25 | 35 | 1,623 | 1,750 |
| | + | 4 | — | 2 | 89 | 95 |
| | p | .0597 | — | .0571 | .0548 | .0543 |
| Nagasaki | n | 342 | 90 | 144 | 6,476 | 7,052 |
| | + | 9 | 5 | 12 | 410 | 436 |
| | p | .0263 | .0556 | .0833 | .0633 | .0618 |
| Total | n | 759 | 241 | 331 | 15,758 | 17,089 |
| | + | 25 | 9 | 16 | 777 | 827 |
| | p | .0329 | .0373 | .0483 | .0493 | .0484 |

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Hiroshima | 2.399 | 3 | .50–.30 |
| Kure | 0.561 | 2 | .80–.70 |
| Nagasaki | 8.890 | 3 | .05–.02 |

of the city differences. The discrepancy in total number of observations between Tables 7 and 8 is due to the exclusion from the latter table of those mothers who were not tested serologically or who gave doubtful serological reactions.

From Table 7, it is apparent that while the cities differ appreciably, there is no evidence that the distribution of economic statuses is markedly different among the classes of parental relationship within a city. In Table 8, the frequency of mothers exhibiting positive serological tests for syphilis is distributed by city and parental relationship. Again, while there are significant differences between cities reflecting socio-economic differences, undoubtedly, there is no evidence that classes of parental relationship differ in the frequency of mothers with positive serological tests. It should be pointed out, however, that a significant negative association between coefficient of inbreeding and frequency of positive serological tests for syphilis can be demonstrated when one disregards the city classification. This does not, however, appear to be an especially meaningful test in view of (1) the demonstrable differences between cities and the disproportionate contribution of the cities to the consanguinity totals, and (2) one cannot demonstrate a significant association when allowance is made for different city intercepts.

In Tables 9 and 10 are given the means and variances for maternal age and parity by city and parental relationship. Here and elsewhere ages have been recorded in the Occidental fashion and to the nearest year. To allow for the disproportionate numbers of observations in the various city-consanguinity cells, analysis of the means has been by the "method of fitting constants". The model on which the main effects were estimated was a "no interaction model". If a significant interaction exists, the main-effects tests are only approximations since they confound interaction (when the within-cells mean square is used as the error variance). In the analysis of the

TABLE 9. MEANS AND VARIANCES FOR MATERNAL AGE BY CITY AND PARENTAL RELATIONSHIP

| Parental Relationship | | Hiroshima | Kure | Nagasaki |
|---|---|---|---|---|
| First cousins | $\bar{x}$ | 27.07 | 28.10 | 28.44 |
| | $s^2$ | 22.50 | 31.10 | 29.78 |
| | n | 936 | 318 | 1,592 |
| First cousins once removed | $\bar{x}$ | 26.86 | 28.12 | 27.95 |
| | $s^2$ | 24.26 | 24.00 | 28.69 |
| | n | 313 | 113 | 412 |
| Second cousins | $\bar{x}$ | 27.26 | 27.79 | 27.80 |
| | $s^2$ | 25.09 | 34.52 | 24.82 |
| | n | 384 | 140 | 637 |
| Unrelated | $\bar{x}$ | 27.24 | 27.92 | 28.60 |
| | $s^2$ | 23.47 | 31.14 | 29.68 |
| | n | 26,012 | 7,544 | 30,240 |

Homogeneity of the means

| Source of Variation | Sum of Squares | DF | Mean Square | F |
|---|---|---|---|---|
| Cities | 27,114 | 2 | 13,557 | 496.59** |
| Relationship | 424 | 3 | 141 | 5.16** |
| Interaction | 269 | 6 | 45 | 1.65 |
| Between classes | 27,654 | 11 | 2,514 | 92.09** |
| Within classes | 1,873,451 | 68,629 | 27.30 | |
| Total | 1,901,105 | 68,640 | | |

Homogeneity of the variances

Bartlett's test $\chi^2 = 497.00^{**}$ DF = 11

TABLE 10. MEANS AND VARIANCES FOR PARITY BY CITY AND PARENTAL RELATIONSHIP

| Parental Relationship | | Hiroshima | Kure | Nagasaki |
|---|---|---|---|---|
| First cousins | $\bar{p}$ | 2.74 | 2.97 | 3.25 |
| | $s^2$ | 2.50 | 3.46 | 4.13 |
| | n | 936 | 318 | 1,592 |
| First cousins once removed | $\bar{p}$ | 2.85 | 3.04 | 3.18 |
| | $s^2$ | 2.81 | 2.97 | 3.72 |
| | n | 313 | 113 | 412 |
| Second cousins | $\bar{p}$ | 2.73 | 2.96 | 3.04 |
| | $s^2$ | 3.29 | 3.45 | 3.37 |
| | n | 384 | 140 | 637 |
| Unrelated | $\bar{p}$ | 2.51 | 2.71 | 3.01 |
| | $s^2$ | 2.40 | 3.31 | 3.46 |
| | n | 26,012 | 7,544 | 30,240 |

Homogeneity of the means

| Source of Variation | Sum of Squares | DF | Mean Square | F |
|---|---|---|---|---|
| Cities | 3,683 | 2 | 1,842 | 605.92** |
| Relationship | 223 | 3 | 74 | 24.34** |
| Interaction | 73 | 6 | 12 | 3.95** |
| Between classes | 3,996 | 11 | 363 | 119.41** |
| Within classes | 208,774 | 68,629 | 3.04 | |
| Total | 212,770 | 68,640 | | |

Homogeneity of the variances

Bartlett's test $\chi^2 = 1{,}078.34^{**}$ DF = 11

concomitant variables, our purpose is not to pursue the effects of these variables, *per se*, but rather to determine whether the various city-consanguinity cells are heterogeneous. Since heterogeneity is established by either a significant interaction or a main effect, we shall not, in the presence of a significant interaction, be concerned about the "best" test of the main effects. In both tables, we note that not only do the means differ significantly between cities but also among classes of parental relationship. Moreover, in the case of parity (or birth rank), the effect of consanguinity is not independent of city effect. In general, mothers who are related to their husbands are younger and have had more pregnancies than those mothers who are unrelated to their husbands. We further note significant differences between city-consanguinity classes with respect to the variances for maternal age and parity. Variation in age of mother exhibits no clear trend with respect to parental relationship, whereas, in the main, there is greater variation in number of pregnancies among related than among the unrelated parents. It can be shown that among these data the proportion of related parents who are of rural origin among all related parents is greater than the proportion of unrelated parents who are of rural origin among all unrelated parents. Since marriages occur somewhat earlier in rural than in urban areas, this may account for the observed differences in mean maternal age and mean number of pregnancies. The occurrence of these differences among classes of parental relationship, whatever their origin, further complicates efforts to dissociate effects of inbreeding from the known effects of maternal age and parity.

To complete the picture of the age stratification of the classes of relationship we present in Tables 11–13 the (1) means and variances for age of father by city and consanguinity, (2) the correlation in age between spouses, and mean differences between mother's age and father's age, and (3) mean age differences among the four types of first-cousin marriages for a sample of approximately 100 marriages of each type. It will be noted that the fathers tend to be younger when related to their spouses although the differences are less striking than for maternal age. Moreover,

TABLE 11. MEANS AND VARIANCES FOR FATHER'S AGE BY CITY AND RELATIONSHIP TO SPOUSE

| City | | Parental Relationship | | | |
|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated |
| Hiroshima | $\bar{x}$ | 32.27 | 32.18 | 32.59 | 32.77 |
| | $s^2$ | 31.84 | 32.95 | 34.25 | 39.51 |
| Kure | $\bar{x}$ | 32.75 | 33.10 | 33.10 | 33.36 |
| | $s^2$ | 37.21 | 35.29 | 41.66 | 44.91 |
| Nagasaki | $\bar{x}$ | 33.28 | 34.20 | 32.95 | 33.85 |
| | $s^2$ | 39.39 | 40.47 | 34.79 | 46.30 |

TABLE 12. THE DISTRIBUTION OF THE MEAN DIFFERENCES BETWEEN MOTHER'S AND FATHER'S AGES AND THE CORRELATION BETWEEN THESE AGES BY CITY AND PARENTAL RELATIONSHIP

| City | | Parental Relationship | | | |
|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated |
| Hiroshima | $\bar{x}$ | 4.68 | 4.74 | 4.87 | 5.04 |
| | $s^2$ | 16.39 | 13.20 | 15.85 | 18.16 |
| | r | 0.69 | 0.75 | 0.72 | 0.70 |
| Kure | $\bar{x}$ | 4.18 | 4.27 | 4.02 | 5.00 |
| | $s^2$ | 13.38 | 11.85 | 13.27 | 16.92 |
| | r | 0.80 | 0.81 | 0.82 | 0.77 |
| Nagasaki | $\bar{x}$ | 4.31 | 5.73 | 4.51 | 4.74 |
| | $s^2$ | 15.23 | 15.40 | 14.43 | 18.79 |
| | r | 0.77 | 0.79 | 0.74 | 0.75 |

TABLE 13. AGE DIFFERENCES BETWEEN SPOUSES IN THE VARIOUS TYPES OF FIRST-COUSIN MARRIAGES

| | Type of first-cousin marriage | | | |
|---|---|---|---|---|
| | Bro-Bro | Sis-Sis | BroSo-SisDa | BroDa SisSo |
| n | 104 | 128 | 103 | 115 |
| Mean | 4.47 | 4.28 | 4.61 | 4.97 |
| Variance | 16.83 | 12.77 | 12.08 | 12.44 |
| Correlation | 0.77 | 0.80 | 0.76 | 0.79 |

Bro-Bro = offspring of brothers
Sis-Sis = offspring of sisters
BroSo-SisDa = brother's son and sister's daughter
BroDa-SisSo = brother's daughter and sister's son

the distributions of fathers' ages are less variable when relationship to the spouse exists than when no relationship exists. The correlation in age between husband and wife tends to be higher when the husband and wife are related although the differences are less marked than the differences between cities within a consanguinity class. Lastly, the mean age differences between spouses for the various types of first-cousin marriages are not significantly different nor, for that matter, are the variance estimates. It is interesting to observe, however, that the average differences in age are greater for cross cousins than for parallel cousins and that less variation of the difference in the age of the spouses exists when they are cross cousins. The age differences reported here are in substantial agreement with those obtained by Ichiba (1953) in a study of consanguineous marriages in four villages in Gifu, Nagano, and Fukushima Prefectures. Ichiba also finds that husband and wife tend to be younger when related and that the difference in ages between spouses is less, being 3.64 years when related and 4.90 years when unrelated.

One other possible difference among classes of parental relationship requires comment, and this is the frequency with which mothers in the various classes have had pregnancies therapeutically interrupted. In the post-war years, Japan, in an effort to control the growth of her population, has relaxed the indications for legal "therapeutic" abortion. At the present time, a pregnancy can be interrupted on any one or combination of three grounds, namely, the pregnancy constitutes a threat to the mother's health, economic distress would result from further children, or there is reason to suspect that the pregnancy may terminate in a child who for one reason or another would be deemed to be an unwelcome addition to society (for more on the

TABLE 14. THE FREQUENCY OF MOTHERS REPORTING ONE OR MORE INDUCED ABORTIONS AT THEIR FIRST REGISTRATION BY CITY AND RELATIONSHIP TO SPOUSE

| City | | Parental relationship | | | | Total |
|---|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated | |
| Hiroshima | n | 625 | 215 | 274 | 17,922 | 19,036 |
| | t | 22 | 10 | 19 | 945 | 996 |
| | p | .0352 | .0465 | .0693 | .0527 | .0523 |
| Kure | n | 239 | 87 | 101 | 5,969 | 6,396 |
| | t | 1 | 2 | — | 52 | 55 |
| | p | .0042 | .0230 | — | .0087 | .0086 |
| Nagasaki | n | 1,074 | 274 | 426 | 20,848 | 22,622 |
| | t | 12 | 4 | 3 | 450 | 469 |
| | p | .0112 | .0146 | .0070 | .0216 | .0207 |
| Total | n | 1,938 | 576 | 801 | 44,739 | 48,054 |
| | t | 35 | 16 | 22 | 1,447 | 1,520 |
| | p | .0181 | .0278 | .0275 | .0323 | .0316 |

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Cities | 464.558 | 2 | <.001 |
| Consanguinity | 13.127 | 3 | <.01 |
| Interaction | 2.602 | 6 | .75–.90 |
| Total | 480.286 | 11 | <.001 |

eugenic aspects see Komai, 1957). In point of fact, the law is sufficiently liberal that the only deterrents to a legal interruption of a pregnancy are the cost and the feeling, held by many, that therapeutic abortions are contrary to family tradition and the natural order of things. Therapeutic interruption of a pregnancy in Japan generally takes the form of dilatation and curettage of the uterus sometime within the first three months of gestation. Conceivably uterine infection and cicatrization following an induced abortion may influence subsequent pregnancy terminations. For this reason, it has seemed advisable to investigate the distribution by parental relationship of mothers reporting one or more therapeutic abortions prior to the pregnancy which led to their registration. These data are presented in Table 14. Significantly fewer induced abortions have occurred to related parents. The significant differences between cities undoubtedly rest on several factors. The lower rate in Kure reflects, without doubt, the fact that the collection of data was terminated not long after the present laws with respect to therapeutic abortions were promulgated, and hence before many women could avail themselves of the new regulations. The low rate in Nagasaki is more difficult to account for but presumably some of the difference between Nagasaki and Hiroshima is attributable to the sizable Roman Catholic population in Nagasaki not present in Hiroshima. The position of the Catholic Church with regard to abortion is well known.

## THE INFLUENCE OF CONSANGUINITY ON THE EFFECTS OF MATERNAL AGE AND PARITY ON PREGNANCY OUTCOME

There exists an extensive literature attesting to the effect of maternal age and parity on pregnancy outcome. Moreover, we have presented elsewhere (Neel and Schull, 1956) evidence that maternal age and/or parity exert a measurable effect on the frequencies of congenital malformations, stillbirths, neonatal deaths, and on birthweight, among infants born in Japan. We ask, now, "Are the effects of maternal age and parity on pregnancy outcome altered by parental relationship?" In view of the demonstrated differences in maternal age and parity among the classes of parental relationship, upon the answer to this question hinges the form of the analysis of the data on pregnancy terminations.

Table 15 presents the distribution of total births and infants congenitally malformed by mother's age and parity for the four classes of parental relationship (cities are pooled). In Table 16 is given the distribution (by maternal age, parity, and relationship) of all infants not known to be malformed and the numbers of such infants who were stillborn or who died in the first seven days of life. It seems unlikely that the combining of stillborn infants with those dying in the first seven days of life will lead to the loss of significant information with respect to maternal age and parity effects. This belief rests on the observations of Yerushalmy (1938, 1945), and Neel and Schull (1956) who found that the general effects of maternal age and parity appear to be the same for stillbirths as for neonatal deaths. Furthermore, since the bulk of deaths occurring in the first seven days of life actually occur in the first twenty-four hours following delivery, before exogenous factors can exert much influence, it seems reasonable to assume that some of the factors contributing to the occurrence of stillbirths also contribute to death in the first seven days of life.

TABLE 15. THE DISTRIBUTION OF MALFORMED INFANTS BY CONSANGUINITY, MATERNAL AGE, AND PARITY

| | Mat. Age | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | m | n | m | n | m | n | m | n | m | n | m | n | m | n | m | n | m | n | m | n | m |
| Unrelated | 15–19 | 1044 | 5 | 155 | 1 | 10 | 0 | 4 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | 1213 | 6 |
| | 20–24 | 9630 | 87 | 5822 | 64 | 1474 | 12 | 272 | 2 | 51 | 0 | 10 | 0 | 1 | 0 | — | — | — | — | — | — | 17260 | 165 |
| | 25–29 | 4962 | 37 | 8538 | 74 | 6449 | 67 | 2645 | 29 | 767 | 8 | 152 | 3 | 30 | 0 | 6 | 1 | — | — | 1 | 0 | 23550 | 219 |
| | 30–34 | 1000 | 10 | 2231 | 22 | 3530 | 46 | 3300 | 21 | 2056 | 33 | 975 | 14 | 302 | 3 | 87 | 1 | 18 | 0 | 13 | 0 | 13512 | 150 |
| | 35–39 | 282 | 3 | 535 | 5 | 869 | 9 | 1145 | 15 | 1260 | 15 | 1078 | 14 | 705 | 6 | 336 | 4 | 151 | 1 | 94 | 1 | 6455 | 73 |
| | 40–44 | 47 | 1 | 95 | 1 | 121 | 3 | 169 | 4 | 193 | 5 | 291 | 8 | 277 | 3 | 222 | 7 | 172 | 3 | 151 | 3 | 1738 | 38 |
| | 45+ | — | — | 1 | 0 | 4 | 0 | 6 | 0 | 7 | 0 | 12 | 0 | 9 | 0 | 10 | 0 | 6 | 0 | 13 | 0 | 68 | 0 |
| | Total | 16965 | 143 | 17377 | 167 | 12457 | 137 | 7541 | 71 | 4334 | 61 | 2518 | 39 | 1324 | 12 | 661 | 13 | 347 | 4 | 272 | 4 | 63796 | 651 |
| First Cousins | 15–19 | 44 | 0 | 8 | 2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 52 | 2 |
| | 20–24 | 351 | 6 | 299 | 2 | 89 | 0 | 14 | 0 | 3 | 0 | — | — | — | — | — | — | — | — | — | — | 756 | 8 |
| | 25–29 | 167 | 4 | 376 | 6 | 323 | 5 | 152 | 1 | 52 | 2 | 14 | 0 | 3 | 0 | 1 | 0 | — | — | — | — | 1088 | 18 |
| | 30–34 | 25 | 0 | 81 | 1 | 127 | 4 | 146 | 1 | 111 | 5 | 57 | 1 | 24 | 1 | 7 | 0 | 3 | 0 | — | — | 581 | 13 |
| | 35–39 | 6 | 0 | 13 | 0 | 26 | 0 | 30 | 0 | 69 | 2 | 49 | 3 | 41 | 1 | 26 | 1 | 15 | 0 | 9 | 0 | 284 | 7 |
| | 40–44 | — | — | 4 | 0 | 3 | 0 | 4 | 0 | 11 | 0 | 9 | 0 | 21 | 0 | 13 | 0 | 4 | 0 | 9 | 0 | 78 | 0 |
| | 45+ | — | — | — | — | — | — | 1 | 0 | 1 | 0 | — | — | — | — | 2 | 0 | 2 | 0 | 1 | 0 | 7 | 0 |
| | Total | 593 | 10 | 781 | 11 | 568 | 9 | 347 | 2 | 247 | 9 | 129 | 4 | 89 | 2 | 49 | 1 | 24 | 0 | 19 | 0 | 2846 | 48 |
| 1½ Cousins | 15–19 | 13 | 0 | 2 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 15 | 1 |
| | 20–24 | 105 | 1 | 109 | 1 | 37 | 1 | 5 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | 256 | 3 |
| | 25–29 | 36 | 0 | 89 | 1 | 100 | 1 | 48 | 0 | 18 | 0 | 5 | 0 | — | — | — | — | — | — | — | — | 296 | 2 |
| | 30–34 | 4 | 0 | 26 | 0 | 42 | 0 | 47 | 0 | 33 | 0 | 12 | 1 | 4 | 0 | 4 | 0 | — | — | — | — | 172 | 1 |
| | 35–39 | 2 | 0 | 3 | 0 | 4 | 0 | 15 | 0 | 19 | 1 | 21 | 0 | 6 | 0 | 4 | 0 | 3 | 0 | 4 | 0 | 81 | 1 |
| | 40–44 | — | — | — | — | — | — | — | — | 1 | 0 | 3 | 0 | 6 | 0 | 2 | 0 | 1 | 0 | 4 | 0 | 17 | 0 |
| | 45+ | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 0 | 1 | 0 |
| | Total | 160 | 1 | 229 | 3 | 183 | 2 | 115 | 0 | 71 | 1 | 41 | 1 | 16 | 0 | 10 | 0 | 4 | 0 | 9 | 0 | 838 | 8 |
| Second Cousins | 15–19 | 25 | 0 | 1 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 26 | 0 |
| | 20–24 | 162 | 2 | 134 | 0 | 33 | 1 | 3 | 0 | 1 | 0 | 2 | 0 | — | — | — | — | — | — | — | — | 335 | 3 |
| | 25–29 | 64 | 1 | 161 | 3 | 130 | 1 | 53 | 2 | 17 | 0 | 4 | 0 | 1 | 0 | — | — | — | — | — | — | 430 | 7 |
| | 30–34 | 9 | 0 | 22 | 0 | 58 | 1 | 67 | 1 | 42 | 1 | 22 | 0 | 8 | 0 | 1 | 0 | 2 | 0 | 1 | 0 | 232 | 3 |
| | 35–39 | 4 | 0 | 4 | 0 | 8 | 0 | 20 | 0 | 25 | 0 | 21 | 0 | 17 | 0 | 8 | 0 | 2 | 0 | 5 | 0 | 114 | 0 |
| | 40–44 | — | — | 3 | 0 | 2 | 0 | 2 | 0 | 1 | 0 | 3 | 0 | 1 | 0 | 4 | 0 | 6 | 0 | 2 | 0 | 24 | 0 |
| | 45+ | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | Total | 264 | 3 | 325 | 3 | 231 | 3 | 145 | 3 | 86 | 1 | 52 | 0 | 27 | 0 | 13 | 0 | 10 | 0 | 8 | 0 | 1161 | 13 |

TABLE 16. THE DISTRIBUTION OF STILLBIRTHS AND NEONATAL DEATHS AMONG INFANTS WITHOUT VISIBLE GROSS MALFORMATION BY CONSANGUINITY, MATERNAL AGE, AND PARITY

| | Mat. Age | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | d | n | d | n | d | n | d | n | d | n | d | n | d | n | d | n | d | n | d | n | d |
| Unrelated | 15–19 | 1039 | 33 | 154 | 3 | 10 | 0 | 4 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | 1207 | 36 |
| | 20–24 | 9543 | 298 | 5758 | 144 | 1462 | 40 | 270 | 10 | 51 | 6 | 10 | 2 | 1 | 1 | — | — | — | — | — | — | 17095 | 501 |
| | 25–29 | 4925 | 193 | 8464 | 187 | 6382 | 156 | 2616 | 66 | 759 | 29 | 149 | 6 | 30 | 1 | 5 | 1 | — | — | 1 | 0 | 23331 | 639 |
| | 30–34 | 990 | 50 | 2209 | 49 | 3484 | 84 | 3279 | 74 | 2023 | 44 | 961 | 23 | 299 | 12 | 86 | 2 | 18 | 1 | 13 | 1 | 13362 | 340 |
| | 35–39 | 279 | 23 | 530 | 19 | 860 | 26 | 1130 | 38 | 1245 | 31 | 1064 | 22 | 699 | 27 | 332 | 9 | 150 | 5 | 93 | 9 | 6382 | 209 |
| | 40–44 | 46 | 5 | 94 | 3 | 118 | 2 | 165 | 2 | 188 | 7 | 283 | 14 | 274 | 14 | 215 | 7 | 169 | 6 | 148 | 6 | 1700 | 66 |
| | 45+ | — | — | 1 | 0 | 4 | 0 | 6 | 0 | 7 | 1 | 12 | 3 | 9 | 0 | 10 | 1 | 6 | 1 | 13 | 1 | 68 | 7 |
| | Total | 16822 | 602 | 17210 | 405 | 12320 | 308 | 7470 | 190 | 4273 | 118 | 2479 | 70 | 1312 | 55 | 648 | 20 | 343 | 13 | 268 | 17 | 63145 | 1798 |
| First Cousins | 15–19 | 44 | 3 | 6 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 50 | 4 |
| | 20–24 | 345 | 14 | 297 | 11 | 89 | 5 | 14 | 1 | 3 | 0 | — | — | — | — | — | — | — | — | — | — | 748 | 31 |
| | 25–29 | 163 | 4 | 370 | 8 | 318 | 10 | 151 | 7 | 50 | 2 | 14 | 2 | 3 | 0 | 1 | 0 | — | — | — | — | 1070 | 33 |
| | 30–34 | 25 | 0 | 80 | 3 | 123 | 5 | 145 | 5 | 106 | 3 | 56 | 0 | 23 | 1 | 7 | 2 | 3 | 0 | — | — | 568 | 19 |
| | 35–39 | 6 | 1 | 13 | 2 | 26 | 1 | 30 | 1 | 67 | 1 | 46 | 1 | 40 | 0 | 25 | 2 | 15 | 2 | 9 | 0 | 277 | 11 |
| | 40–44 | — | — | 4 | 1 | 3 | 0 | 4 | 0 | 11 | 0 | 9 | 0 | 21 | 1 | 13 | 0 | 4 | 0 | 9 | 0 | 78 | 2 |
| | 45+ | — | — | — | — | — | — | 1 | 0 | 1 | 0 | — | — | — | — | 2 | 0 | 2 | 0 | 1 | 0 | 7 | 0 |
| | Total | 583 | 22 | 770 | 26 | 559 | 21 | 345 | 14 | 238 | 6 | 125 | 3 | 87 | 2 | 48 | 4 | 24 | 2 | 19 | 0 | 2798 | 100 |
| 1½ Cousins | 15–19 | 13 | 1 | 1 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 14 | 1 |
| | 20–24 | 104 | 5 | 108 | 3 | 36 | 2 | 5 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | 253 | 10 |
| | 25–29 | 36 | 2 | 88 | 1 | 99 | 5 | 48 | 0 | 18 | 0 | 5 | 0 | — | — | — | — | — | — | — | — | 294 | 8 |
| | 30–34 | 4 | 0 | 26 | 2 | 42 | 1 | 47 | 0 | 33 | 0 | 11 | 0 | 4 | 0 | 4 | 0 | — | — | — | — | 171 | 3 |
| | 35–39 | 2 | 0 | 3 | 0 | 4 | 0 | 15 | 0 | 18 | 0 | 21 | 0 | 6 | 0 | 4 | 0 | 3 | 0 | 4 | 0 | 80 | 0 |
| | 40–44 | — | — | — | — | — | — | — | — | 1 | 0 | 3 | 0 | 6 | 0 | 2 | 0 | 1 | 0 | 4 | 0 | 17 | 0 |
| | 45+ | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 0 | 1 | 0 |
| | Total | 159 | 8 | 226 | 6 | 181 | 8 | 115 | 0 | 70 | 0 | 40 | 0 | 16 | 0 | 10 | 0 | 4 | 0 | 9 | 0 | 830 | 22 |
| Second Cousins | 15–19 | 25 | 1 | 1 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 26 | 1 |
| | 20–24 | 160 | 3 | 134 | 1 | 32 | 2 | 3 | 0 | 1 | 0 | 2 | 0 | — | — | — | — | — | — | — | — | 332 | 6 |
| | 25–29 | 63 | 3 | 158 | 4 | 129 | 4 | 51 | 1 | 17 | 2 | 4 | 0 | 1 | 0 | — | — | — | — | — | — | 423 | 14 |
| | 30–34 | 9 | 0 | 22 | 0 | 57 | 3 | 66 | 5 | 41 | 1 | 22 | 0 | 8 | 1 | 1 | 0 | 2 | 0 | 1 | 0 | 229 | 10 |
| | 35–39 | 4 | 0 | 4 | 0 | 8 | 0 | 20 | 2 | 25 | 1 | 21 | 1 | 17 | 1 | 8 | 0 | 2 | 0 | 5 | 0 | 114 | 5 |
| | 40–44 | — | — | 3 | 0 | 2 | 0 | 2 | 0 | 1 | 0 | 3 | 0 | 1 | 0 | 4 | 0 | 6 | 2 | 2 | 0 | 24 | 2 |
| | 45+ | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | Total | 261 | 7 | 322 | 5 | 228 | 9 | 142 | 8 | 85 | 4 | 52 | 1 | 27 | 2 | 13 | 0 | 10 | 2 | 8 | 0 | 1148 | 38 |

As is apparent from Tables 15 and 16, the data are not sufficient to allow sophisticated treatment of the influence of consanguinity on the effects of maternal age and parity on the occurrence of congenital malformations or perinatal deaths, that is, death during parturition or in the first seven days thereafter. However, since it is unlikely that a larger body of data than these will be immediately forthcoming, it would seem appropriate to explore, in at least a preliminary fashion, the question of the association of maternal age and parity effects with consanguinity.

Figures 1–3 relate the frequency of abnormal pregnancy terminations with maternal age, parity, and parity for specified maternal age. To obtain a greater measure of stability in the variable, we have resorted to two devices, namely, the combination of (1) perinatal deaths and congenital malformations as abnormal pregnancy terminations, and the combination of (2) terminations occurring to first cousins once removed and to second cousins. Two features of these data warrant singling out for comment. Firstly, at all ages, or parities where the numbers of terminations are fairly large, there occur more abnormal terminations among the pregnancies of first cousins than among those of unrelated individuals. The frequency of abnormal terminations among "first cousins once-removed and second cousins" is more or less intermediate between the unrelated and first-cousin groups. Secondly, the general shape of the maternal age or parity curves is surprisingly similar for first cousins and unrelated parents. Greater instability is shown in the combined first-cousins-once-removed and second-cousin group; however, the values for this latter group tend to fluctuate between the other two groups. It would appear that if consanguinity exerts any influence on the effects of maternal age and parity the effect is small.

It may be argued that combining congenital malformations with perinatal deaths when the effects of maternal age and parity are not the same, or at least do not appear to be the same, would obfuscate an association of consanguinity with maternal age and parity effects. In this connection, it is worth noting that the curves for perinatal deaths alone though exhibiting greater instability are substantially the same as Figures 1–3. Moreover, since the ratio of perinatal deaths to congenital malformations is reasonably constant over the classes of parental relationship, it seems reasonable to assume that whatever distortion may arise from pooling would be proportional.

We have presented elsewhere (Neel and Schull, 1956) evidence that among the offspring of unrelated parents the effects of maternal age and parity on birthweight, as measured in tens of grams, can be adequately approximated by a regression of the form

$$\hat{y} = m + b_1x + b_2w + b_3z$$

where

$\hat{y}$ = birthweight
m = mean birthweight
x = parity
w = parity squared
z = maternal age

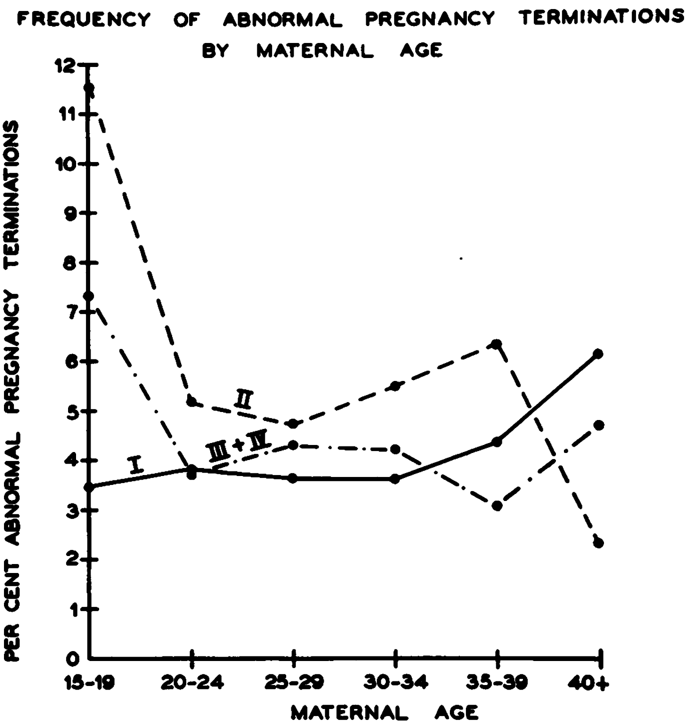


FIG. 1. The distribution of the frequency of abnormal pregnancy terminations by maternal age for the pregnancies of unrelated parents (I), first cousins (II), and first cousins once removed plus second cousins (III and IV).

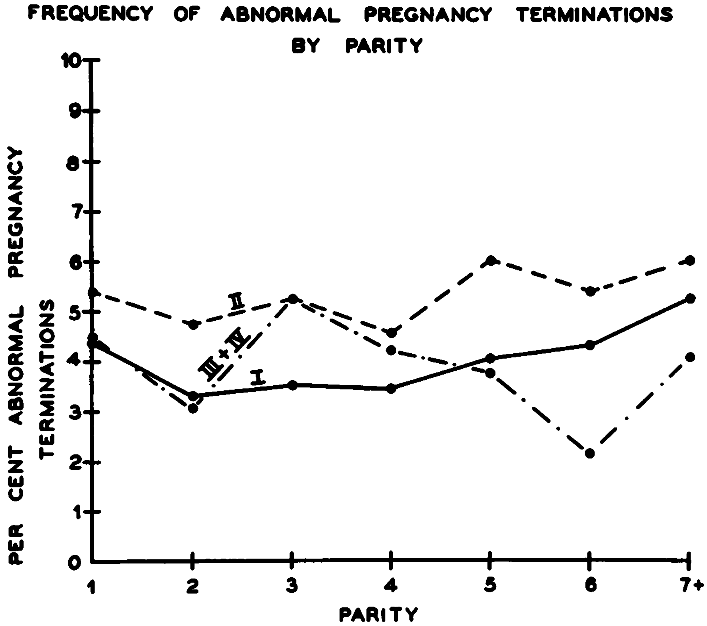


FIG. 2. The distribution of the frequency of abnormal pregnancy terminations by parity (birth rank) for the pregnancies of unrelated parents (I), first cousins (II), and first cousins once removed plus second cousins (III and IV).

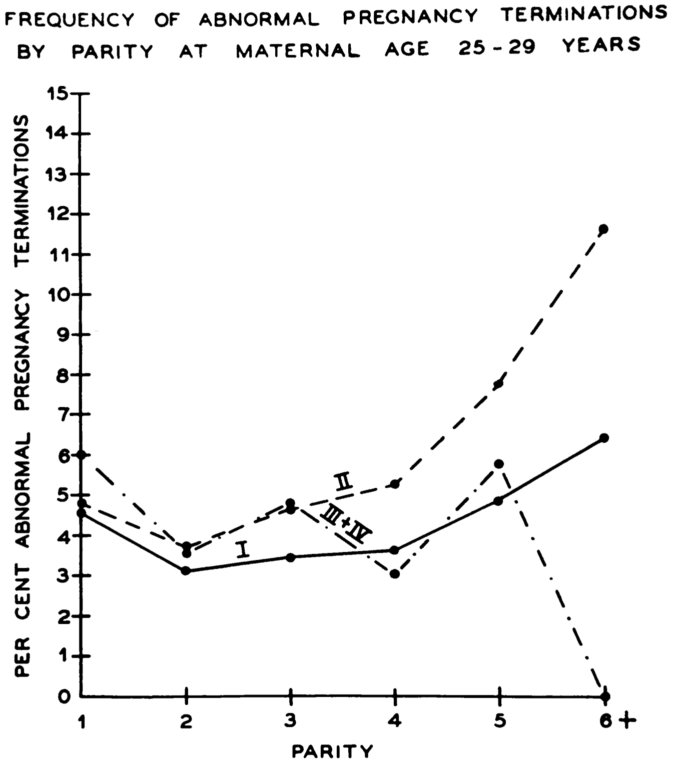


FIG. 3. The distribution of the frequency of abnormal pregnancy terminations by parity fo mothers 25–29 years old among the different classes of parental relationship (unrelated—I; firs cousins—II; first cousins once removed plus second cousins—III and IV).

and $b_1$, $b_2$, and $b_3$ are respectively the regression coefficients associated with parity, parity squared, and maternal age. Millis and Seng (1954) have shown that this same relationship is applicable to infants born in Singapore in the period 1950–1951.

It can be shown that if regressions of the type just described are fitted to the 12 city-consanguinity classes considering sexes separately and taking into account differences between the city-consanguinity classes in average birthweight, age, etc., the estimates of the regression coefficients from the various city-consanguinity classes are not significantly heterogeneous. The common regression equation for males is

$$\hat{y}_{ijk} = \bar{y}_{ij} + 9.188(x_{ijk} - \bar{x}_{ij}) - 0.672(w_{ijk} - \bar{w}_{ij}) - 0.192(z_{ijk} - \bar{z}_{ij})$$

and for females is

$$\hat{y}_{ijk} = \bar{y}_{ij} + 8.309(x_{ijk} - \bar{x}_{ij}) - 0.611(w_{ijk} - \bar{w}_{ij}) - 0.238(z_{ijk} - \bar{z}_{ij}).$$

The $\bar{y}_{ij}$, $\bar{x}_{ij}$, $\bar{w}_{ij}$, and $\bar{z}_{ij}$ are, respectively, the means in the $ij^{th}$ city-consanguinity cell for birthweight, parity, parity squared, and maternal age. The regression coefficients are decagram increases (or decreases) in birthweight for unit changes in parity, maternal age, etc. Since the regression coefficients are not significantly heterogeneous, consanguinity does not appear to alter the relationship of maternal age and parity to birthweight. This is perhaps not surprising since the component of variation in birthweight ascribable to genetic factors in the fetus is small (Robson 1955, Morton, 1955).

### THE EFFECT OF INBREEDING ON THE SEX RATIO

If there exist partially sex-linked lethal genes in man, one might expect an alteration in the sex ratio among the offspring of related parents. It has been shown that if related marriages occur at random, with respect to the four sex combinations through whom the relationship of husband and wife is traced, there will exist an excess of homozygous females (for details see Macklin, 1952). The amount of the excess, under random mating, is a function of the frequency of recombination of the locus in question with sex. In the absence of random mating, the ratio of affected females to affected males will be a function not only of the frequency of recombination but also of the true proportions of the four sex combinations through whom parental relationship occurs. Morton (1955) has shown that the different mating types of first cousins, first cousins once removed, and second cousins are non-randomly distributed in the Japanese. The departure from randomness, at least with respect to first-cousin matings, is not, however, sufficient to alter markedly the ratio of affected females to affected males from that obtaining under an assumption of random occurrence of the mating types.

Inspection of Table 17, where the distribution of male infants by city and parental relationship is given, fails to reveal any clear trends which might be construed as evidence for the existence of partially sex-linked lethal genes. Analysis of these data (see Table 18) reveals no significant effect of inbreeding on the frequency of male births.

In Table 18 and in the succeeding tables dealing with the analysis of the attributes of children born to related parents, we have presented or will present two analyses. Firstly, there is a chi-square analysis by the method of Roy and Kastenbaum (1956;

TABLE 17. THE DISTRIBUTION OF MALE INFANTS BY CONSANGUINITY AND CITY

| City | | Parental relationship | | | | Total |
|---|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated | |
| Hiroshima | n | 936 | 313 | 384 | 26,012 | 27,645 |
| | ♂ | 478 | 153 | 196 | 13,550 | 14,377 |
| | p | .5107 | .4888 | .5104 | .5209 | .5201 |
| Kure | n | 318 | 113 | 140 | 7,544 | 8,115 |
| | ♂ | 151 | 60 | 78 | 3,872 | 4,161 |
| | p | .4748 | .5310 | .5571 | .5133 | .5128 |
| Nagasaki | n | 1,592 | 412 | 637 | 30,240 | 32,881 |
| | ♂ | 837 | 233 | 325 | 15,689 | 17,084 |
| | p | .5258 | .5655 | .5102 | .5188 | .5196 |
| Total | n | 2,846 | 838 | 1,161 | 63,796 | 68,641 |
| | ♂ | 1,466 | 446 | 599 | 33,111 | 35,622 |
| | p | .5151 | .5322 | .5159 | .5190 | .5190 |

TABLE 18. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF MALE INFANTS AND CONSANGUINITY

a. Chi-square analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Cities | 1.435 | 2 | .30–.50 |
| Consanguinity | .803 | 3 | .80–.90 |
| Interaction | 8.086 | 6 | .10–.25 |
| Total | 10.324 | 11 | .50–.70 |

b. Regression analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Regression | 0.052 | 1 | .75–.90 |
| Residual | 0.765 | 2 | .50–.75 |
| Sum | 0.817 | 3 | |

see also Roy and Mitra, 1956). If in this analysis significant differences between cities or a significant interaction of city with consanguinity obtains, then the regression analysis, the second method to be used, will be designed to allow for different city intercepts (means). If there is no demonstrable difference between cities nor an interaction between city and consanguinity, then the regression analysis will be based on the pooled consanguinity data. In the Roy and Kastenbaum method (see Roy and Mitra, 1956), the chi-squares associated with the "main effects" and "interaction" are independently distributed, but additivity is only in probability and asymptotically as $n \rightarrow \infty$. We have, therefore, computed the "interaction" in two ways, namely, (1) by formally solving the appropriate equations, and (2) by subtracting from the total chi-square the sum of the "main effects." In the tables, we have presented only the larger of these two chi-squares. This would seem to be a conservative procedure in that while one probably errs in asserting heterogeneity more frequently than it exists, the sole consequence of this is a more laborious regression analysis.

The regression analysis involves the fitting of a weighted regression of the natural logarithm of the proportion of survivors, or males, or non-malformed infants, as the case may be, on F, the coefficient of inbreeding. The genetic argument underlying this regression model is set forth in a paper by Morton, Crow, and Muller, 1956, and the basis on which the weights were computed will be found in Fisher's *Design of Experiments* (Section 68). It should, perhaps, be pointed out that in testing the fit of the regression model we have assumed that the various sums of weighted sums of squares of deviations from the mean, from the regression formula, and the reduction in the sums of squares of deviations in the dependent variable attributable to the regression are distributed as chi-square. While it can be shown that this is true for a normally distributed variable, when the weights are the informations with respect to the parameters being estimated, here, for a variety of reasons, an element of approximation exists. For convenience, the means and regression coefficients obtained by fitting this model to the data on sex ratio, malformations, and mortality are presented only once, and then in summary, in Table 35. In the Japanese data, as in the French data analyzed by Morton, Crow, and Muller, the simple approximation $S = 1 - A - BF$ yields substantially the same slope B, and intercept, A, as obtained by fitting to S, the proportion of survivors, an exponential curve. We shall routinely test the common regression against a one-tailed alternative. In the case of the individual regressions, we shall also test against a one-tailed alternative provided the regression coefficients are all of the same sign. Since a test of the heterogeneity of the individual regression coefficients is sensitive to the magnitude of the coefficients as well as their signs, it may occur that a one-tailed test will be employed where the regression coefficients are clearly heterogeneous in magnitude but not in sign. This would not seem inappropriate since the regressions may agree in indicating an effect of consanguinity, but differ in the estimation of its importance. Clearly, two different questions are at stake.

## THE EFFECT OF INBREEDING ON THE INCIDENCE OF MAJOR CONGENITAL MALFORMATIONS

Major congenital malformations are defined as those departures from normality which are incompatible with life or seriously limit the functioning of the individual, either directly or indirectly. Obviously, in the application of this definition to a series of malformations an element of subjectivity enters—there is no absolute division between "major" and "minor" malformations. We consider the malformations listed in Table 19 to be major congenital anomalies. Other patently major abnormalities which may occur to the reader either did not occur in this series of births, or, if they occurred, were unrecognized.

The distribution of infants with major congenital abnormalities by city and consanguinity will be found in Table 20. The frequency of infants with major congenital malformations increases significantly with increasing inbreeding (see Table 21). It would not appear that this association of consanguinity with the frequency of infants with major congenital defects is explicable in terms of residual maternal age and parity variation. The same general trend observable in Table 20 is clearly visible in Table 15 within those parity and age-specific cells where the entries are sufficiently numerous in all consanguinity classes to permit a judgment (e.g., parity 1 and maternal age 20–24 or parity 2 and maternal age 25–29).

The significant association of consanguinity with malformation rate suggests that some of the abnormalities listed in Table 19 arise as a consequence of homozygosity for a recessive gene or genes. We now ask, "Is it possible to form some judgment as to which malformations may be due to recessive genes?" In Table 22, the twelve most frequently occurring diagnoses are tabulated by parental relationship (a detailed presentation of the malformations found among the inbred and outbred children is presented elsewhere; see Neel, 1958, and Schull, 1958). Among the uncomplicated diagnoses, no one abnormality *clearly* suggests recessive factors. Complex anomalies appear, however, to be more frequent among the children of related parents. Conceivably some of the complex abnormalities are in fact hitherto unrecognized syndromes; if this is true, presumably some of these syndromes would have relatively simple modes of inheritance. Thus, it may be that the increase in the frequency of complex abnormalities reflects the increased probability of homozygosity for one

TABLE 19. AN ALPHABETICAL LISTING OF THOSE MALFORMATIONS OBSERVED IN THIS STUDY WHICH, OCCURRING ALONE OR IN COMBINATION WITH ONE ANOTHER, WERE GRADED AS MAJOR CONGENITAL DEFECT (AFTER NEEL AND SCHULL, 1956)

Achondroplasia
Albinism
Amputation, congenital
Anencephaly
Anonychia
Anophthalmos
Arthrogryposis
Atresia ani or rectum
Atresia of the external nares

Blepharophimosis
Brachydactyly

Cataracts
Central nervous system defect, severe
Claw hand
Cleft palate
Club foot
Coloboma iridis
Corneal defect
Cryptophthalmia
Cystic hygroma

Diaphragm, defect of
Diastasis recti, severe
Dislocations, multiple, congenital
Dysplasia of acetabulum, congenital

Ectodermal defect, congenital
Ehlers-Danlos syndrome
Encephalocele
Exostosis, severe, of bone
External ear, major malformation of

Facial cleft, oblique
Flexion deformity of fingers and toes
Foetus amorphous
Foetus papyraceous
Funnel chest

Gastroschisis

Harelip
Heart disease, congenital, cyanotic
Hemimelus
Hydrocephalus
Hypertelorism
Hypospadias, marked

Ichthyosis, congenita
Inguinal hernia (females)
Intestinal obstruction, congenital

Lymphangioma

Macroglossia
Major bone, absence of
Malformation, complex and ill-defined
Microcephaly
Micropenis
Microphthalmus
Microtia
Mongolism

Neurofibromatosis
Nystagmus, congenital

Oligodactyly
Omphalocele

Polydactyly
Polyostotic fibrous dysplasia
Polyoty
Ptosis of eyelids
Pupillary membrane, persistent

Radio-ulnar synostosis
Recto-vaginal fistula
Rhinencephaly

Situs inversus viscerum
Spina bifida with or without meningocele or meningomyelocele
Status Bonnevie-Ullrich
Sympodia
Syndactyly
Synorchism

Teratoma
Thyroglossal duct, persistent
Tumor, type undetermined

TABLE 20. THE DISTRIBUTION OF INFANTS WITH MAJOR CONGENITAL ABNORMALITIES BY CONSANGUINITY AND CITY

| City | | Parental relationship: First Cousins | 1½ Cousins | Second Cousins | Unrelated | Total |
|---|---|---|---|---|---|---|
| Hiroshima | n | 936 | 313 | 384 | 26,012 | 27,645 |
| | m | 17 | 2 | 4 | 293 | 316 |
| | p | .0182 | .0064 | .0104 | .0113 | .0114 |
| Kure | n | 318 | 113 | 140 | 7,544 | 8,115 |
| | m | 4 | 2 | 1 | 58 | 65 |
| | p | .0126 | .0177 | .0071 | .0077 | .0080 |
| Nagasaki | n | 1,592 | 412 | 637 | 30,240 | 32,881 |
| | m | 27 | 4 | 8 | 300 | 339 |
| | p | .0170 | .0097 | .0126 | .0099 | .0103 |
| Total | n | 2,846 | 838 | 1,161 | 63,796 | 68,641 |
| | m | 48 | 8 | 13 | 651 | 720 |
| | p | .0169 | .0095 | .0112 | .0102 | .0105 |

TABLE 21. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF CONGENITAL MALFORMATIONS AND CONSANGUINITY

a. Chi-square analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Cities | 7.269 | 2 | .02–.05 |
| Consanguinity | 11.775 | 3 | .001–.01 |
| Interaction | 2.535 | 6 | .75–.90 |
| Total | 21.525 | 11 | .02–.05 |

b. Regression analysis*

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Individual regressions | 7.262 | 3 | .02–.05 |
| Common regression | 2.957 | 1 | .02–.05 |
| Heterogeneity | 4.305 | 2 | .10–.25 |
| Residual | 2.663 | 6 | .75–.90 |
| Sum within cities | 9.925 | 9 | |

* In the absence of significant heterogeneity, one-tailed tests of significance will be used for the common and individual regressions.

or more recessively inherited, rare syndromes. Unfortunately, the data are not sufficiently numerous to permit a critical appraisal of this hypothesis.

It is interesting to note, at this point, that Yanase (1951) in his report on Shībamura also found multiple abnormalities in individuals born of a consanguineous marriage to be not infrequent. Haldane (1951) advanced evidence that unlinked genes may be associated as a consequence of the inbreeding which occurs in man. Whether the increase in multiple abnormalities reported here is a manifestation of the association of unlinked genes or represents pleiotropy cannot be determined with the data at hand.

There remains one other observation on the frequency of congenital malformation in these data worth considering, and this is the extent to which the observed associa-

TABLE 22. THE DISTRIBUTION OF TWELVE OF THE MORE COMMON AT-BIRTH DIAGNOSES BY CONSANGUINITY. FREQUENCIES ARE GIVEN AS THE NUMBER OF AFFECTED INFANTS PER 10,000 BIRTHS

| Diagnosis | Parental relationship | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | First Cousins | | 1½ Cousins | | Second Cousins | | Unrelated | | |
| Club foot | 3 | 10.5 | — | — | 1 | 8.6 | 59 | 9.2 | 63 |
| Polydactyly | 1 | 3.5 | 1 | 11.9 | — | — | 38 | 6.0 | 40 |
| Syndactyly | — | — | — | — | — | — | 12 | 1.9 | 12 |
| Polydactyly-syndactyly | — | — | — | — | — | — | 11 | 1.7 | 11 |
| Oligodactyly | 2 | 7.0 | — | — | — | — | 5 | 0.8 | 7 |
| Dysplasia of acetabulum | 1 | 3.5 | 1 | 11.9 | — | — | 16 | 2.5 | 18 |
| Atresia ani | 1 | 3.5 | — | — | 1 | 8.6 | 5 | 0.8 | 7 |
| Harelip with or without cleft palate | 5 | 17.6 | 3 | 35.8 | 2 | 17.2 | 120 | 18.8 | 130 |
| Simple cleft palate | 6 | 21.1 | — | — | — | — | 29 | 4.5 | 35 |
| Anencephalus | 1 | 3.5 | — | — | — | — | 34 | 5.3 | 35 |
| Anophthalmus and/or microphthalmus | 2 | 7.0 | — | — | — | — | 13 | 2.0 | 15 |
| Hydrocephalus | 2 | 7.0 | — | — | — | — | 11 | 1.7 | 13 |
| Complex anomaly including two or more of the above | 3 | 10.5 | — | — | — | — | 25 | 3.9 | 28 |
| Complex anomaly including one or more of the above* | 6 | 21.1 | 1 | 11.9 | 3 | 25.8 | 46 | 7.2 | 56 |
| Other | 18 | 63.2 | 2 | 23.9 | 6 | 51.7 | 252 | 39.5 | 278 |

* With the exception of this group, all groups are mutually exclusive.

tion of inbreeding and malformation rate may be due to sex-linked recessive genes. The pertinent data arise as follows: Among the four classes of first-cousin marriages, an opportunity for homozygous females to occur due to the combination of derivatives of a gene present in one of the common ancestors exists only when the father and mother are the offspring of two sisters, or when the father is the son of a woman whose brother is the father of the mother. In these two instances, the coefficient of inbreeding with respect to sex-linked genes would be greater than zero; whereas, in the remaining two classes of first-cousin marriages, F would be zero. If the X-chromosome is contributing in any significant degree to the malformations here measured, then we may expect the malformation rate among the *female* offspring of spouses who are related as the children of sisters, or the son of a sister and the daughter of the sister's brother, to be greater than when the spouses are offspring of brothers or the daughter of a sister and the son of the sister's brother. In Hiroshima and Nagasaki combined, we have information on 190 pregnancies where the method of relationship of the parents is known, and where the pregnancy terminated in a female infant. The distribution of malformed infants is as follows:

| | Type of First Cousins | | | | |
|---|---|---|---|---|---|
| | Sis-Sis | Bro-Bro | SisSo-BroDa | SisDa-BroSo | Total |
| Malformed | 7 | 3 | 4 | 3 | 17 |
| Normal | 50 | 34 | 51 | 38 | 173 |
| Total | 57 | 37 | 55 | 41 | 190 |

Two comments on these data are in order. Firstly, the malformation rate observed is not indicative of the malformation rate in the general population of related mar-

TABLE 23. THE DISTRIBUTION OF EARLY DEATHS BY CITY AND CONSANGUINITY. FOR A DEFINITION OF EARLY DEATHS REFER TO THE TEXT

| City | | Parental relationship | | | | Total |
|---|---|---|---|---|---|---|
| | | First Cousins | 1½ Cousins | Second Cousins | Unrelated | |
| Hiroshima | N | 919 | 311 | 380 | 25,719 | 27,329 |
| | d | 46 | 16 | 19 | 810 | 891 |
| | p | .0501 | .0514 | .0500 | .0315 | .0326 |
| Kure | N | 314 | 111 | 139 | 7,486 | 8,050 |
| | d | 13 | 1 | 7 | 265 | 286 |
| | p | .0414 | .0090 | .0504 | .0354 | .0355 |
| Nagasaki | N | 1,565 | 408 | 629 | 29,940 | 32,542 |
| | d | 66 | 8 | 18 | 1,016 | 1,108 |
| | p | .0422 | .0196 | .0286 | .0339 | .0340 |
| Total | N | 2,798 | 830 | 1,148 | 63,145 | 67,921 |
| | d | 125 | 25 | 44 | 2,091 | 2,285 |
| | p | .0447 | .0301 | .0383 | .0331 | .0336 |

riages because a long form, with the subsequent opportunity to determine the method of relationship, exists only on every tenth pregnancy termination, and every abnormal pregnancy termination. This series is, then, loaded with malformations, but the loading should be random if sex-linked genes are not involved in the etiology of the malformations observed. Secondly, from inspection of the data, it seems possible that the X-chromosome may be exerting a small effect since the malformation rate is 9.82 per cent when $F \neq 0$ and 7.69 per cent when $F = 0$. This difference, though in the direction specified by the hypothesis, is not significant.

## THE EFFECT OF INBREEDING ON THE FREQUENCY OF EARLY DEATHS

For our purposes, we shall define early death as death during parturition or in the first month of life thereafter. Early deaths include, then, infants who were stillborn or who died in the first month of life, and *did not exhibit visible, gross abnormalities.*

The distribution of early deaths by city of birth and parental relationship is given in Table 23. From inspection of this table, it will be noted that, in general, the frequency of early deaths increases with increasing inbreeding. It will also be noted, however, that this apparent association of inbreeding and early death is not equally striking in the three cities. These impressions are borne out by analysis of the data (see Table 24). We see that the individual regressions remove a significant amount of variation, as does the common regression, but that the individual regressions are significantly heterogeneous. In short, though the cities are consistent in revealing an effect of inbreeding, they are inconsistent in revealing the magnitude of the effect. The reasons for this heterogeneity are not clear. One can, of course, ascribe it to sampling variation, but it is conceivable that the heterogeneity stems from residual variation in concomitant variables influencing pregnancy outcome. We shall return to these data shortly, and consider whether the same heterogeneity exists if one partitions early deaths into (a) stillbirths, and (b) livebirths terminating in death in the first thirty days of life.

Table 24. Analysis of the relationship between the frequency of early death and consanguinity

a. Chi-square analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Cities | 1.954 | 2 | .25–.50 |
| Consanguinity | 12.108 | 3 | .001–.01 |
| Interaction | 14.462 | 6 | .01–.025 |
| Total | 28.524 | 11 | <.001 |

b. Regression analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Individual regressions* | 10.959 | 3 | <.01 |
| Common regression* | 2.924 | 1 | <.05 |
| Heterogeneity | 8.035 | 2 | .01–.025 |
| Residual | 10.289 | 6 | .10–.25 |
| Sum within cities | 21.247 | 9 | |

* One-tailed test.

Table 25. The distribution of deaths in the first nine months of life by city and consanguinity

| City | | Parental relationship: First Cousins | 1½ Cousins | Second Cousins | Unrelated | Total |
|---|---|---|---|---|---|---|
| Hiroshima | n | 335 | 107 | 139 | 8,606 | 9,187 |
| | d | 24 | 4 | 8 | 392 | 428 |
| | p | .0716 | .0374 | .0576 | .0455 | .0466 |
| Nagasaki | n | 487 | 125 | 177 | 8,725 | 9,514 |
| | d | 30 | 1 | 10 | 416 | 457 |
| | p | .0616 | .0080 | .0565 | .0477 | .0480 |
| Total | n | 822 | 232 | 316 | 17,331 | 18,701 |
| | d | 54 | 5 | 18 | 808 | 885 |
| | p | .0657 | .0216 | .0570 | .0466 | .0473 |

### THE EFFECT OF INBREEDING ON INFANTILE AND CHILDHOOD MORTALITY

As has been previously indicated, a sample of the infants seen at birth was selected for examination in the central clinical facility at the age of nine months. This second observational period permits extending the data on mortality to include the first nine months of life as well as the perinatal period.

Inspection of Table 25, where the distribution of deaths in the first nine months of life is given by city and consanguinity, suggests the possibility of an association; however, it will be noted that in both cities there is an apparent depression of the death rate among the children born to parents related as first cousins once removed. In Table 26 are given the results of analyzing these data. The consanguinity classes differ significantly one from another, and there is no city difference nor evidence of city-consanguinity heterogeneity. It would be appropriate, therefore, to measure the effect of inbreeding on the pooled city data. When this is done, one notes that

TABLE 26. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF DEATH IN THE FIRST NINE MONTHS OF LIFE AND CONSANGUINITY

a. Chi-square analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Cities | 0.217 | 1 | .50–.75 |
| Consanguinity | 10.411 | 3 | .01–.02 |
| Interaction | 1.769 | 3 | .50–.75 |
| Total | 12.397 | 7 | |

b. Regression analysis

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Regression* | 3.290 | 1 | .025–.05 |
| Residual | 5.175 | 2 | .05–.10 |
| Sum | 8.465 | 3 | |

* One-tailed test.

TABLE 27. THE DISTRIBUTION OF THE SAMPLE SELECTED FOR STUDY IN HIROSHIMA IN 1956 BY CONSANGUINITY

| Consanguinity | Recontacted | Moved from city | Unable to locate | Total |
|---|---|---|---|---|
| First cousins | 352 | 35 | 32 | 419 |
| 1½ cousins | 106 | 17 | 13 | 136 |
| Second cousins | 144 | 13 | 18 | 175 |
| Unrelated | 567 | 74 | 78 | 719 |
| Total | 1169 | 139 | 141 | 1449 |

the regression does remove a significant amount of variation. There exists, then, a significant association of inbreeding with mortality in the first nine months of life.

Still a third body of data exists on the relationship of consanguinity to mortality. In the summer of 1956, an attempt was made in a selected sample to determine the frequency of death in the first eight years of life. For this purpose, 1500 pregnancy registrations were selected in Hiroshima. These registrations were selected from the years 1948–1949, and represented (a) the first 750 liveborn children to be recorded in the genetics program whose parents were related, and (b) the first 750 liveborn "zero" infants (infants whose registration numbers terminated in zero) whose parents were unrelated. After selection, multiple births were excluded leaving 1490 infants in Hiroshima to be studied. An effort was then made to revisit the parents of these infants to determine whether the child was still alive, and if not alive, the cause and date of death. In Table 27 are presented the numbers of successful and unsuccessful attempts to revisit for the various classes of parental relationship. Inspection of this table reveals several items of interest. Firstly, it should be noted that the related parents show a lower migration rate than that exhibited by the unrelated parents. This may be a manifestation of the same sense of family unity which motivated these individuals to select relatives for their spouses. Secondly, among the unsuccessful attempts to revisit within each class of relationship, approximately half are cases where the parents are known to have moved from the city and the other half could not be located.

TABLE 28. THE DISTRIBUTION OF MATERNAL AGE AMONG RELATED AND UNRELATED PARENTS WHO WERE OR WERE NOT CONTACTED IN 1956

Hiroshima

| Group | n | $\bar{x}$ | $s^2$ |
|---|---|---|---|
| Contacted: | | | |
| Related parents | 601 | 27.09 | 28.15 |
| Unrelated parents | 565 | 27.72 | 28.12 |
| Not contacted: | | | |
| Related parents | 128 | 25.95 | 26.34 |
| Unrelated parents | 152 | 26.23 | 22.35 |

Homogeneity of the means

| Source | S.S. | DF | M.S. | F |
|---|---|---|---|---|
| Relationship | 95.59 | 1 | 95.59 | 3.49 |
| Contact | 378.77 | 1 | 378.77 | 13.84** |
| Interaction | 25.59 | 1 | 25.59 | 1.07 |
| Between classes | 499.96 | 3 | 166.65 | 6.09** |
| Within classes | 39,470.37 | 1,442 | 27.37 | |
| Total | 39,970.33 | 1,445 | | |

Homogeneity of the variances

$\chi^2 = 3.398$ DF = 3

In view of the differential rates of attrition among the related and unrelated parents, to draw valid inferences from the data collected requires demonstrating that the migrating individuals do not differ appreciably from the non-migrating persons, or if differences do exist that such differences are the same among the related and unrelated parents. Some data relevant to this point exist. In Table 28 are given the results of comparing, for the related and unrelated groups, the ages of mothers who have remained in the city with the ages of those who have moved from the city or cannot now be located (the disparity between this table and Table 27 is due to the exclusion of 3 mothers whose ages were not recorded at the follow-up). It is to be noted that while mothers who have moved from the city are, on the average, significantly different in age (younger) than those who have not moved, there is no indication from the interaction that this age difference is dissimilarly distributed in the related and unrelated groups. Equivalent findings can be demonstrated with regard to the mean number of pregnancies experienced by related and unrelated mothers living in and outside the city. The age and parity differences obtaining among the related and unrelated parents would appear to be such as to lead to an inflation of the death rate particularly in the first year of life among the offspring of unrelated parents. Residual concomitant variation may, then, minimize the significance of the data on mortality in the first eight years of life.

In Table 29 are distributed the deaths in the first eight years of life by parental relationship. At a glance, it would appear that childhood mortality is associated with inbreeding in Hiroshima. Upon analysis of these data (see Table 30), we find a significant association of the variable with consanguinity. In an attempt to reenforce this finding, Table 31 is presented (a small discrepancy between Tables 29 and 31 exists because of the failure to record age at death for one of the children born to first cousins once removed). In this table, it will be noted that the deaths occurring

TABLE 29. THE DISTRIBUTION OF DEATHS IN THE FIRST EIGHT YEARS OF LIFE IN HIROSHIMA BY CONSANGUINITY

| | Parental Relationship | | | | |
|---|---|---|---|---|---|
| | First Cousins | 1½ Cousins | Second Cousins | Unrelated | Total |
| Total infants | 352 | 106 | 144 | 567 | 1,169 |
| Deaths | 41 | 9 | 8 | 31 | 89 |
| Proportion | .1165 | .0849 | .0556 | .0547 | .0761 |

TABLE 30. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF DEATH IN THE FIRST EIGHT YEARS OF LIFE AND CONSANGUINITY

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Regression | 10.119 | 1 | <.001 |
| Residual | 0.432 | 2 | .75–.90 |
| Sum | 10.552 | 3 | .01–.025 |

TABLE 31. A PARTITION OF DEATHS IN THE FIRST EIGHT YEARS OF LIFE IN HIROSHIMA

| | Death in first year | | | Death between 1–8 years of life | | |
|---|---|---|---|---|---|---|
| Consanguinity | n | d | p | n | d | p |
| First cousins | 352 | 26 | 0.0739 | 326 | 15 | 0.0460 |
| 1½ cousins | 106 | 5 | 0.0472 | 101 | 3 | 0.0297 |
| Second cousins | 144 | 5 | 0.0347 | 139 | 3 | 0.0216 |
| Unrelated | 567 | 23 | 0.0406 | 544 | 8 | 0.0147 |
| Total | 1,169 | 59 | 0.0505 | 1,110 | 29 | 0.0261 |

in the first eight years of life have been partitioned into two groups, namely, deaths in the first year, and deaths between years 1 and 8 of life. Now we may surmise that deaths in the first year of life should agree reasonably well with the values obtained in the first nine months of life (see Table 25) if the inbreeding effect here observed is real. From a comparison of Tables 25 and 31, we see that the two different estimates are sensibly the same. It is equally clear that the results obtained at eight years of age are not wholly explicable in terms of the effect of inbreeding on death in the first year of life. Inbreeding effects are not confined, then, to a single stage in life.

Before we attempt to summarize the data on the association of inbreeding with infantile and childhood mortality, let us return to the data on early deaths and examine the results of partitioning these data into (a) stillbirths, and (b) neonatal deaths, i.e., deaths in the first month of life. In Table 32 is given the distribution of stillborn infants by city and parental relationship. The distribution of neonatal deaths, which will not be presented, can be obtained by the reader by subtracting the number of stillborn infants in each city-consanguinity cell from the number of infants at risk and from the number of early deaths in that cell as given in Table 23. Inspection of Table 32 suggests that in Kure and Nagasaki the effect of inbreeding on the frequency of stillborn infants is small and contrary to the genetic hypothesis. Hiroshima, however, supports the notion of an appreciable inbreeding effect. Analysis of these data (see Table 33a) fails to reveal heterogeneity among the regression coefficients, or that a significant amount of variation is removed by either the common

TABLE 32. THE DISTRIBUTION OF STILLBORN INFANTS BY CITY OF BIRTH AND PARENTAL RELATIONSHIP

| City | | Parental relationship: First Cousins | 1½ Cousins | Second Cousins | Unrelated | Total |
|---|---|---|---|---|---|---|
| Hiroshima | n | 919 | 311 | 380 | 25,719 | 27,329 |
| | s | 19 | 6 | 6 | 345 | 376 |
| | p | .0207 | .0192 | .0158 | .0134 | .0138 |
| Kure | n | 314 | 111 | 139 | 7,486 | 8,050 |
| | s | 5 | 1 | 4 | 144 | 154 |
| | p | .0159 | .0090 | .0288 | .0192 | .0191 |
| Nagasaki | n | 1,565 | 408 | 629 | 29,940 | 32,542 |
| | s | 22 | 3 | 9 | 443 | 477 |
| | p | .0141 | .0074 | .0143 | .0148 | .0147 |
| Total | n | 2,798 | 830 | 1,148 | 63,145 | 67,921 |
| | s | 46 | 10 | 19 | 932 | 1,007 |
| | p | .0164 | .0120 | .0166 | .0148 | .0148 |

TABLE 33. a. ANALYSIS OF THE RELATIONSHIP OF INBREEDING TO THE FREQUENCY OF STILLBIRTHS

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Individual Regressions* | 3.457 | 3 | .12-.25 |
| Common Regression* | 0.061 | 1 | .37-.45 |
| Heterogeneity | 3.396 | 2 | .10-.25 |
| Residual | 2.767 | 6 | .75-.90 |
| Sum (within cities) | 6.224 | 9 | |

b. ANALYSIS OF THE RELATIONSHIP OF INBREEDING TO THE FREQUENCY OF NEONATAL DEATH

| Source | $\chi^2$ | DF | P |
|---|---|---|---|
| Individual Regressions* | 10.425 | 3 | .001-.01 |
| Common Regression* | 3.649 | 1 | .025-.05 |
| Heterogeneity | 6.776 | 2 | .025-.05 |
| Residual | 9.522 | 6 | .10-.25 |
| Sum (within cities) | 19.947 | 9 | |

* One-tailed test.

regression or the pooled individual regressions. The common regression coefficient is positive, and therefore in the direction of the hypothesis of an inbreeding effect. Analysis of the neonatal death data (see Table 33b) proves to be very much like the findings for early deaths in that (1) all of the regression coefficients are positive, (2) the common regression and the individual regressions remove a significant amount of variation, and (3) the individual regressions, though all positive, are significantly different in magnitude. It would appear, however, that removal of the stillbirths has somewhat reduced the heterogeneity from that in the case of the early deaths. This latter statement is based on the heterogeneity tests in the two instances.

One final observation regarding the data on stillbirths and neonatal deaths seems pertinent. If one compares the stillbirth rate among the pregnancies of unrelated parents with that obtaining among the pregnancies of related parents (all classes of consanguineous marriages pooled) for each city and year (ignoring the year 1954 in Hiroshima and Nagasaki), one finds that among the fifteen possible comparisons the stillbirth rate among the offspring of related parents exceeds that among the offspring of unrelated parents in only eight instances. This number of exceedances is clearly not significant on a sign test. A similar analysis of the neonatal death rates, on the other hand, reveals that in twelve of fifteen comparisons the death rate is higher among the offspring of related parents. This is clearly significant on a sign test. The data are, then, internally consistent in revealing an effect of inbreeding on neonatal mortality while failing to reveal an effect of inbreeding on the frequency of stillbirths.

We are faced with the problem of accounting for the heterogeneity between cities in the effects of inbreeding on the frequency of stillbirths and neonatal deaths. With respect to the latter variable, the heterogeneity is, perhaps, not too difficult to rationalize. One may argue for the existence of differences in the regression coefficients as follows: In a certain sense, most, if not all, "genetic deaths" involve the interaction of a specific genotype with environmental factors. Clearly we may visualize a spectrum of interactions ranging from, say, what might be termed absolute deaths (the genotype is incompatible, with any known environment) to situations where the genotype is compatible, in at least some degree, with all environments. Amelioration of the environmental factors which in association with a specific genotype leads to death should produce a relatively greater reduction in deaths among the offspring of parents who are related, than among the offspring of parents who are unrelated, since the requisite genotype is proportionately more frequent. This would, of course, lead to a decline in the value of the regression coefficient. During periods of rapid and substantial improvement in the environment, a temporal trend in the value of the regression coefficient might be demonstrable. In view of the known differences between Hiroshima, Kure, and Nagasaki, it is not at all inconceivable that amelioration may have occurred in different ways and to different extents in the three cities. One may argue, as a matter of fact, that identical estimates would be most unexpected since this would require that the mean fitness of these three populations, with reference to the loci measured, be the same. On an *a priori* basis, this would be hard to believe in view of the differences in the concomitant variables affecting mortality, and the possible genetic differences in these three groups of people.

The heterogeneity with respect to the stillbirth data admits of several intriguing explanations. Perhaps, the most conservative one proceeds as follows: Clearly the survival of a liveborn child depends upon the genotype of that child and the environmental stresses to which it is subject. The survival, however, of a fetus is a much more complex phenomenon involving the interaction of fetal genotype, maternal genotype, and maternally mediated environmental factors. In this nexus of interactions, it is possible that the stillbirth component attributable to fetal genotype is overshadowed by the maternal genotype and environmental stresses mediated through the mother. This overshadowing of the fetal genotype could result in a failure to detect an inbreeding effect on stillbirths when an inbreeding effect on neonatal mortality was clearly demonstrable. Moreover, an amelioration of the maternally mediated environmental stresses in one area but not in others could result in a detection of an inbreeding effect in one city not demonstrable in the others. Furthermore, it is conceivable that this amelioration of environmental stresses mediated through the mother could occur independently of any amelioration of the environmental stresses on the liveborn child, and, as a consequence, one might find a relatively high association of inbreeding and stillbirth in conjunction with an equally high, or higher association of inbreeding and neonatal mortality.

To summarize the mortality data, we find the following:

(1) The role of inbreeding in the etiology of stillbirths cannot clearly be determined from these data. Hiroshima suggests an effect of inbreeding on the stillbirth rate; whereas Kure and Nagasaki fail to reveal an association between these two variables. In Kure and Nagasaki not only are the regression coefficients not significantly different from zero, but the estimates are actually negative in sign.

(2) A significant, positive association of inbreeding with death in the first month of life appears in all three cities. The magnitude of this effect varies from one city to another presumably due to environmental differences and/or residual concomitant variation.

(3) In the first 9 months of life, Hiroshima and Nagasaki are consistent in proclaiming an effect of inbreeding on mortality during this period of life.

(4) Finally, evidence from Hiroshima suggests that inbreeding continues to exert a measurable influence on mortality beyond the first year of life and to the eighth year of life, the upper age limit of this study.

## THE INFLUENCE OF INBREEDING ON PREGNANCY WASTAGE AS MEASURED BY ANAMNESTIC DATA

One further approach to the problem of the relationship of consanguinity to pregnancy termination remains to be discussed. It has been argued that since (1) offspring of consanguineous marriages run an increased risk of homozygosity for deleterious recessive mutants, and since (2) homozygosity for such mutations may be manifested as abortions occurring before the mother is aware of her pregnancy, the mean interval between the beginning of cohabitation for a couple and the termination of the first recognizable pregnancy may bear a relationship to the biological relatedness of the cohabiting couple. To explore this possibility all first-born children were tabulated by parental relationship and the interval, in months, between the registration of the pregnancy and the beginning of cohabitation on the part of the parents. These data are presented in Table 34. Obviously to draw inferences from these data requires certain assumptions. Among the most important of these are (1) whatever element of family planning there is in Japan, it is the same in all classes of parental relationship; (2) the beginning of cohabitation is accurately and reliably reported in all classes of relationship; and (3) the interval between eligibility to register and actual registration is the same in all consanguinity classes. It is patently impossible to assert that these assumptions are fulfilled by the data or that they are not fulfilled. We have seen, for example, that there is evidence that the various consanguinity classes differ with regard to the frequency of mothers reporting therapeutic interruptions. Since a therapeutic interruption of a pregnancy is a socially acceptable means of regulating family size in Japan, we may interpret the observed differences among the consan-

TABLE 34. MONTHS OF COHABITATION PRIOR TO THE REGISTRATION OF FIRST PREGNANCY

| Months | Parental Relationship | | | |
|---|---|---|---|---|
| | First Cousins | 1½ Cousins | Second Cousins | Unrelated |
| 1 | 1 | 1 | — | 24 |
| 2 | 1 | — | — | 18 |
| 3 | — | — | — | 56 |
| 4 | 26 | 8 | 8 | 721 |
| 5 | 54 | 14 | 25 | 1,998 |
| 6 | 72 | 20 | 30 | 2,114 |
| 7 | 52 | 18 | 26 | 1,816 |
| 8 | 51 | 15 | 23 | 1,612 |
| 9 | 41 | 8 | 16 | 1,281 |
| 10 | 38 | 16 | 18 | 1,055 |
| 11 | 35 | 7 | 13 | 862 |
| 12 | 31 | 7 | 11 | 742 |
| 13 | 22 | 2 | 11 | 610 |
| 14 | 13 | 8 | 9 | 480 |
| 15 | 18 | 5 | 6 | 413 |
| 16 | 14 | 6 | 13 | 365 |
| 17 | 12 | 6 | 8 | 309 |
| 18 | 6 | 3 | 5 | 259 |
| 19 | 6 | 2 | 3 | 240 |
| 20 | 7 | 1 | 3 | 186 |
| 21–22 | 13 | 6 | 10 | 318 |
| 23–24 | 15 | 2 | 4 | 265 |
| 25–26 | 9 | — | 4 | 191 |
| 27–28 | 6 | 1 | 3 | 145 |
| 29–30 | 10 | 2 | 5 | 135 |
| 31–32 | 6 | — | 2 | 95 |
| 33–34 | 1 | 2 | 1 | 82 |
| 35–36 | 3 | 1 | 1 | 73 |
| 37–38 | 3 | — | — | 65 |
| 39–40 | 6 | 1 | — | 75 |
| 41–42 | 5 | — | 1 | 58 |
| 43–44 | 4 | — | 1 | 46 |
| 45–46 | 4 | — | 1 | 42 |
| 47–48 | 1 | — | 1 | 40 |
| 49–50 | 1 | 1 | 3 | 29 |
| 51–52 | 4 | — | 1 | 23 |
| 53–54 | 2 | — | — | 23 |
| 55–56 | 1 | — | — | 22 |
| 57–58 | — | — | — | 20 |
| 59+ | 8 | 2 | 2 | 291 |
| Total | 602 | 165 | 268 | 17,199 |

guinity classes as evidence of differences in family planning or, perhaps, in notions of the desirable size of family. The fact that differences do obtain need not necessarily vitiate the approach proposed since the observed differences would appear to lengthen the interval in the unrelated class. This would seem to follow for we know that frequently pregnancies which occur very shortly after marriage are interrupted so that the wife may continue to work until a greater measure of economic security is attained. Because of the higher frequency of induced abortions among the unrelated parents presumably more first pregnancies are also interrupted. These cases would not enter the present tabulation which is restricted to first pregnancies where the gestation was of at least 21 weeks duration. The net effect would be to exclude a proportionately greater number of very short intervals among the unrelateds than among the relateds with the consequent increase in the mean interval for the unrelated parents. This would, of course, tend to minimize a consanguinity effect, if present.

One of the major factors determining the lag between eligibility to register a pregnancy and actual registration must be economic, reflecting the need for the supplementary rations, etc. which are available upon registration. Since marked differences in the distribution of economic statuses among parental relationships do not obtain, we may surmise that motivation is similar among the classes, and presumably the intervals between eligibility and actual registration would be similar. These speculations do not, of course, establish that the assumptions enumerated above are met by these data, but they do afford one some measure of confidence that the assumptions may be approximately fulfilled.

Inspection of Table 34 fails to reveal any striking differences among the classes of relationship. We note that in all four instances the modal interval is six months. The means and medians show some slight shift to the right when the parents are related; however, the magnitude of the shift bears no clear relationship to the coefficient of inbreedings as can be seen from the following figures:

| | Median | Mean |
|---|---|---|
| Unrelated parents | 9 | 12.19 months |
| First Cousins | 10 | 13.56 months |
| 1½ Cousins | 9 | 11.92 months |
| Second Cousins | 10 | 13.05 months |

In view of the smallness of the differences among the consanguinity classes and the largeness of the sources of concomitant variation, it seems doubtful that one can attribute the observed shifts to a consanguinity effect with much measure of assurance.

## OTHER STUDIES IN JAPAN ON THE EFFECTS OF CONSANGUINEOUS MARRIAGES

It is informative at this juncture to review briefly some of the Japanese studies on the effects of consanguinity since virtually all of these studies are inaccessible to workers outside Japan for reasons of language.

In general, the Japanese studies have taken one or the other of two forms. As has been indicated, a number of investigations have been made on the so-called "consanguinity villages" in Japan, and information of a variety of sorts has been collected. Within the "consanguinity villages" since virtually all individuals are related to some degree, and since degree of inbreeding has often not been considered, analysis of the data has involved the comparison of the results obtained in the "consanguinity village" with an adjacent village where consanguineous marriages are uncommon, or with the values characteristic of the prefecture in which the village is situated. A second type of study has involved villages or towns sufficiently large that a comparison of children whose parents were unrelated with children whose parents were related is possible. Regression methods have not been employed in analyzing any of these studies, and the published accounts of the data preclude the use of such methods by others. The samples of related individuals available for study have generally been small regardless of the method of study.

Two Japanese studies appear especially germane to the data presented here, namely, the work of Ichiba (1953, 1954) on school age children in Gifu, Nagano and Fukushima Prefectures and the work of Shiroyama (1953) and Shiroyama and Shiroyama (1953) on pre-school age and school age children in Miyazaki Prefecture.

Ichiba has studied 2,829 children in grades 1 to 6 living in Itadori, Gifu; Ina, Nagano; Katagiri, Nagano; Okisawa, Fukushima; and Sekihara, Tokyo. Of this number, 190 children are of consanguineous parents. A rather extensive array of anthropometric, physiological and psychological measures was obtained. Among the measurements were chest width, chest breadth, chest length, length of sternum, length of trunk, head girth, pelvis width, neck girth, abdominal girth, waist girth, head width, span, chest angle, sitting height, grasping power, 50 meter run, Tanaka Type B Intelligence Test, and appraisals of temperament. The effect of consanguinity was assayed by converting the observed measures on the 2,829 children to standard measure and then observing whether the measurements on the consanguineous group were uniformly distributed around zero. For the fourteen anthropometric measurements in every instance more than fifty per cent of the children born to consanguineous marriages exhibit measurements which are less than the average for the 2,829 children who were investigated. For each of the two physiological measures, more than fifty per cent of the children of related parents were below the means of the whole group. Finally, on the intelligence test a greater percentage of the children of consanguineous parents were found to be dull than was true of the children of unrelated parents. Ichiba infers that there may be a general shift of the I.Q. distribution since the extremes of the I.Q. distributions are not appreciably different for the two classes of children. Ichiba summarizes his data by asserting that the effects of consanguinity on the variables which he studied must be small if existent at all.

Shiroyama (1953), in a study conducted in Kiyotake-mura, Miyazaki Prefecture, in 1948, obtained birthweights, heights, weights, and chest circumferences on 121 children (63♂) born to related parents in the years 1943–1948, and on 858 children (430♂) born to unrelated parents in the same time period. He failed to demonstrate significant differences in birthweight, chest girth, height, or weight. However, it is interesting to note that of the fourteen possible comparisons between the children of related and unrelated parents when sex and year of birth are taken into account in 11 instances the mean birthweight for the child of consanguineous parents is less than the mean birthweight of the child of unrelated parents.

In another study, Shiroyama and Shiroyama (1953) investigated the mental development of some 374 children of whom 48 were the offspring of related parents. A significantly greater proportion of the children of related parents exhibited I.Q.s of less than 70 than was true among the children of unrelated parents (related: 8 out of 48; unrelated: 19 out of 326; $\chi^2 = 7.338$, DF = 1).

Shinozaki (1955), Shinozaki and Aoki (1951), and Shinozaki, Yoshida, and Aoki

(1951) have reported results obtained from the investigation of three "consanguinity villages." These are Narata to which previous reference has been made, Nanaura and Hata buraku of Toyobusa-mura in Chiba Prefecture, and Akiyamagō which lies partly in Nagano and partly in Niigata Prefecture. Narata and Akiyamagō are mountain villages of 957 and about 1200 persons respectively; Nanaura and Toyobusa-mura are coastal, fishing-farming villages of about 5,241 individuals. The economies of Narata and Akiyamagō are marginal and the general nutritional status is poor. Nanaura and Toyobusa-mura, on the other hand, enjoy an appreciably better economy, and food is ample, if not abundant. The studies were conducted in 1943 (Narata), 1948 (Akiyamagō), and 1950 (Nanaura and Toyobusa-mura). In all three instances, the authors advance evidence suggesting a lowered birth rate; thus, the birth rate in Narata was 29 per 1000 at a time when the national average was 35 (1940), Akiyamagō had a birth rate of 26.4 when the national average was 33.8 (1948). The data for Nanaura and Toyobusa-mura are presented as Pearl's "rate of pregnancy," and the values obtained were 33.6 for related parents and 43.9 for unrelated parents. Stature was below normal in Narata and Akiyamagō, but equal to the national average in Nanaura and Toyobusa-mura. In all three studies, however, physical capacity as measured by grasping power, strength of back muscles, etc. was below normal. The onset of menstruation was 16–17 years in Narata, 15.6 years in Akiyamagō, and 15.3 years in Nanaura and Toyobusa-mura as contrasted with the national average of about 14.6 years. No unusual incidence of clearly inherited recessive, autosomal or sex-linked, pathologies was found in Narata or Nanaura. In Akiyamagō, on the other hand, 24 per cent of the males and 2 per cent of the females exhibited red-green colorblindness.

One other study which deserves mentioning is the work of Yanase (1951). Yanase studied the physical well-being of individuals residing in four villages in Western Japan with relatively high rates of consanguineous marriage. These villages were Shība-mura, Miyazaki Prefecture; Kariya-mura, Yamaguchi Prefecture; Shika-mura and Shikanoshima-mura, Fukuoka Prefecture. Shība-mura and Shika-mura are mountain villages whereas Shikanoshima-mura and Kariya-mura are coastal villages. Yanase finds that each of these villages has its own quantitative and qualitative peculiarities. Thus, Shība-mura exhibits a relatively high frequency (5.4 per cent) of heterochromia iridis not found in the other villages; cataracts and lateral epicanthus are common in Shikanoshima-mura. Moreover, within Shība-mura, specific abnormalities have restricted geographical distributions, and though the defects occur more frequently among the offspring of consanguineous marriages they are found among the offspring of individuals not known to be related. Among the offspring of individuals not known to be related, the frequency is higher when both parents come from the same *aza* than when both parents are drawn from the same *chiku*. Neither the *chiku* nor the *aza* are regular units of measure in the sense, say, that the terms township and section, where used in the United States, define fixed areas of land, namely, 36 and 1 square mile respectively. As a general rule, a *chiku* is larger than an *aza*.[4]

[4] Japanese terms such as *aza*, *chiku*, *buraku*, etc. are no less confusing than their English counterparts, and are equally defiant of rigid definition. The term *mura* is applied to an administrative

### AN ESTIMATE OF THE MUTATIONAL DAMAGE IN MAN

Recently several different methods for estimating the mean number of deleterious mutants in man which homozygously would lead to the death of an individual between birth and maturity have been advanced (see Slatis, 1954; Morton, Crow, and Muller, 1956; Krooth, 1957). All of these methods employ, as the basis of estimation, the detrimental effects of consanguineous marriage.

Morton, Crow, and Muller (1956) estimate that, on the basis of data collected by Sutter and Tabah (1953, 1954), Arner (1908), and Bemiss (1858), "the average gamete carries a group of detrimental factors that, if dispersed in separate individuals and made homozygous, would result in 1.5–2.5 deaths of that age group. Thus the total genetic damage here measured is 1.5–2.5 lethal equivalents per gamete, or 3–5 per zygote." A lethal equivalent is defined as "a group of mutant genes of such number that . . . they would cause on the average one death, e.g., one lethal mutant, or two mutants with 50 per cent probability of causing death, etc."

Several tests for internal consistency of the various collections of consanguinity data were made by Morton, Crow, and Muller, 1956. We reproduce, for comparative purposes, their findings with regard to the data of Sutter and Tabah whose study was more nearly comparable to the Japanese than those of Arner or Bemiss. The regression coefficients B, $B_{FF}$, $B_{FO}$, and $B_{CO}$ reproduced in Table 35 are, respectively, the regression coefficients obtained by using (1) all different degrees of consanguinity (unrelated, second cousins, 1½ cousins, and first cousins), (2) the different degrees of consanguinity omitting completely the noninbred group, (3) the noninbred group and the average of all inbred groups, and (4) the noninbred and the first cousin marriages only. In Table 35, we also present the corresponding values obtained in Hiroshima, Kure, and Nagasaki. Within these data, comparison of $B_{FF}$ with $B_{FO}$ affords a measure of internal consistency. Only the early death data from Hiroshima and Nagasaki are inconsistent by this criterion. No single explanation appears to account for this inconsistency.

To compare meaningfully the entries in Table 35, certain differences in definition and method of data collection between the French and Japanese studies must be borne in mind. Thus,

1. The French study was retrospectively oriented, and involved a sample of marriages contracted in a given time period, 1920–21 in the district of Morbihan, and 1919–25 in the district of Loir-et-Cher. The Japanese study was prospectively oriented, and included virtually all of the marriages producing a pregnancy lasting for at least five months during 1948–1954 in Hiroshima, Nagasaki and Kure. Sutter and Tabah have investigated a more or less sedentary population which was rural to rural-urban; the study in Japan encompasses a definitely urban area and a some-

village. The *mura* may be subdivided, area-wise, into *Ōaza* or *aza* which need not be and generally are not, of equal size. Frequently the population encompassed by a *mura* will not be continuously distributed over the area which the *mura* includes. There exists an opportunity, then, for discrete collections of houses which in English might be termed hamlets, but, in Japanese, are *buraku*. The *chiku* merely refers to an area in the same vague sense in which we might speak of the northwest section of a city.

TABLE 35. A COMPARISON OF THE EFFECTS OF INBREEDING IN JAPAN WITH THOSE FOUND IN FRANCE

| Source of data | A | B | B/A | $B_{FF}$ | $B_{FO}$ | $B_{CO}$ |
|---|---|---|---|---|---|---|
| *Morbihan* | | | | | | |
| Stillbirths-neonatal deaths | .0460 | 1.124 | 24.43 | .901 | 1.233 | 1.163 |
| Infant-juvenile deaths | .0950 | 1.431 | 15.06 | .937 | 1.665 | 1.222 |
| Total | .1410 | 2.555 | 18.12 | | | |
| *Loir-et-Cher* | | | | | | |
| Stillbirths-neonatal deaths | .0335 | .574 | 17.12 | .398 | .662 | .538 |
| Infant-juvenile deaths | .0558 | .908 | 16.26 | 1.201 | .759 | 1.141 |
| Total | .0893 | 1.482 | 16.60 | | | |
| *Hiroshima* | | | | | | |
| Malformations | .0113 | .084 | 7.43 | .193 | .062 | .112 |
| Early deaths | .0322 | .371 | 11.52 | −.007 | .432 | .310 |
| Death in 9 months | .0465 | .395 | 8.49 | .450 | .383 | .444 |
| Death in 8 years | .0543 | 1.076 | 19.82 | 1.392 | .982 | 1.082 |
| Total* | .0763 | 1.231 | 16.13 | | | |
| *Kure* | | | | | | |
| Malformations | .0077 | .099 | 12.86 | .071 | .104 | .079 |
| Early deaths | .0360 | .044 | 1.22 | .042 | .042 | .100 |
| Total | .0437 | .143 | 3.27 | | | |
| *Nagasaki* | | | | | | |
| Malformations | .0099 | .108 | 10.91 | .114 | .107 | .115 |
| Early deaths | .0343 | .091 | 2.65 | .355 | .034 | .138 |
| Death in 9 months | .0487 | .144 | 2.96 | .373 | .096 | .235 |
| Total* | .0722 | .234 | 3.24 | | | |

* The totals are derived from summing malformations, death in 8 years (or in 9 months in the case of Nagasaki), and that component of early deaths due to stillbirths.

what more mobile population. Information on the inbred and outbred groups was obtained in different fashions in the case of Sutter and Tabah's study; this was not true for the work in Japan.

2. In the Japanese study, each marriage is represented, on the average, by 1–2 children whereas in the French data each marriage is represented by about 3.5–4.5 children, on the average.

3. Stillbirths and neonatal deaths, in the French data, include late miscarriages, stillbirths, and deaths in the first month of life. Conspicuous abnormality may or may not have been present. Early deaths in the Japanese study include late miscarriages, stillbirths, and deaths in the first month of life without conspicuous abnormality.

4. Infantile and juvenile deaths in the French data include deaths from one month of age to, presumably, the maximum age which might be attained by the offspring of parents who had been married 25–30 years. Death in 9 months or death in 8 years in our data include deaths among liveborn, non-malformed infants at any time after birth until 9 months or 8 years as the case may be. There are, of course, numerous other differences between the studies most of which are functions of the different cultural milieu in which the studies were conducted. The effect of these differences on the data cannot be readily evaluated.

Any comparison of the values given in Table 35 is not without danger. In the strict sense, the estimates of A and B have meaning only with reference to the particular set of environmental circumstances obtaining in the areas under consideration. And certainly there is no reason for believing that the environmental stresses in Loir-et-Cher or Morbihan are the same, or even similar, to those in Hiroshima, Kure, or Nagasaki. Clearly, then, a comparison of the absolute values of A and B has little meaning. A somewhat more meaningful comparison involves the ratio of B to A. The latter may be viewed as an index of the relative importance of inbreeding. In a comparison of the values in Table 35, the ratio B to A obtained from summing malformations and early deaths in Hiroshima and Nagasaki is to be compared with the values obtained for stillbirths-neonatal deaths in Morbihan or Loir-et-Cher. Similarly, the total for Hiroshima should be roughly comparable to the totals for Morbihan or Loir-et-Cher; whereas the total for Nagasaki, since data on only the first nine months of life are available, might be expected to range between the values for stillbirths-neonatal deaths and the totals for the two French areas. We note that the ratio of B to A obtained for Hiroshima compares favorably with those for Morbihan and Loir-et-Cher. Nagasaki, on the other hand, exhibits a value appreciably different from the other three areas. This is, of course, not unexpected in view of the discrepancies between Hiroshima and Nagasaki previously pointed out.

If one accepts the assumptions on which Morton, Crow, and Muller (1956) base their estimate of the total mutation rate for lethals and detrimentals in man, and if the differing periods of risk in Japan and France are taken into account, then the "total" rate of mutations in Hiroshima, for mutations expressing themselves in a fashion here measurable, would be substantially the same as those obtained by Morton, Crow, and Muller from the French data, namely, 0.03–0.06 mutants per gamete or $3\text{–}6 \times 10^{-6}$ per locus per generation. Nagasaki, however, would suggest a value only one-third to one-fourth as high. More reliable estimates of our "load of mutations" require (1) a better understanding of the average dominance of nominally recessive, deleterious genes in man, and (2) measurement of a wider spectrum of mutants than has thus far been possible in man. With regard to the former, our knowledge is so scanty that Morton, Crow, and Muller had to draw upon Drosophila data in order to estimate the mutation rate given above. Morton (personal communication) has indicated that the assumption that the average dominance of deleterious genes in man is the same as in Drosophila has been troublesome; moreover, even in Drosophila the data rest on a special class of recessives, namely, lethals. Efforts are currently underway to remedy the second deficiency enumerated by reinvestigating the children reported in this paper at ages 5–10. At this time, a wide battery of clinical, biochemical, anthropometric, and psychometric measures are to be obtained. It may be presumed that this more detailed examination of the children of consanguineous matings will reveal hitherto unmeasured genetic damage.

## SUMMARY

Data on the effect of inbreeding on the sex ratio, and the frequencies of major congenital malformations, early deaths (stillbirths and neonatal deaths), deaths in the first nine months of life, and death in the first eight years of life have been presented. These data were collected in Hiroshima, Nagasaki, and Kure, Japan during the years 1948–1956 under the joint sponsorship of the Atomic Bomb Casualty Commission of the National Academy of Sciences-National Research Council of the United States and the National Institute of Health of Japan.

The prevalence of consanguineous marriages and the marriage practices which appear to maintain the relatively high degree of inbreeding in Japan are discussed. It is shown that consanguineous marriages vary in frequency and type in Hiroshima, Nagasaki, and Kure, and, at least with respect to Hiroshima and Nagasaki, the frequency of consanguineous marriages is clearly on the decline.

Among the socio-economic factors measured, consanguineous marriages do not differ significantly from non-consanguineous marriages with respect to economic level or frequency of positive serology among parturient mothers. Consanguineous marriages do differ significantly, however, from non-consanguineous marriages with regard to (1) maternal age, (2) parity, (3) paternal age, and (4) the frequency of "therapeutic" interruption of pregnancies.

Biological relationship of husband and wife does not appear to alter the effects of maternal age and parity on pregnancy outcome, nor can one demonstrate a significant effect of inbreeding on the sex ratio. Inbreeding does, however, significantly alter the frequency of major congenital malformations. Interestingly, a rather substantial portion of the increase in congenital malformations with increasing inbreeding is due to the occurrence of complex or multiple major malformations.

In these data, an unequivocal effect of inbreeding on early deaths cannot be demonstrated; this failure to demonstrate a consistent effect of inbreeding rests on demonstrable city heterogeneity. Hiroshima, Kure and Nagasaki are consistent in revealing an increasing death rate with increasing inbreeding; the heterogeneity arises in connection with the magnitude of this effect. Hiroshima and Nagasaki are in agreement in revealing an effect of inbreeding on mortality in the first 9 months of life, and Hiroshima reveals that this effect is still demonstrable after the first year of life.

No clear effect of inbreeding on the interval between cohabitation and the first recognizable pregnancy is demonstrable, and hence there is no evidence that the increased risk of homozygosity for deleterious genes among the children of related parents is manifested as early fetal loss and an apparent difficulty in establishing a successful pregnancy.

The results of this study are compared with the findings of other workers in Japan, and especially the findings of Sutter and Tabah in France. A general level of agreement is established.

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