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The Effect of Inbreeding on Mortality in Japan[1]

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A century ago, in the midst of a flurry of interest in consanguineous marriages, the Philadelphia Ledger observed, " If one half is true that has been affirmed in regard to the effect of cousins intermarrying, it would seem as if it were the duty of parents and guardians to interfere, and even of all State Legislatures to do what can be done to prevent so injurious a custom ". These sentiments were sufficiently widespread to be echoed in an editorial in the Times of India, dated August 9, 1860, and they might well be justified today if we could establish that, in fact, " one half that is affirmed is true ". Interests in the effect of consanguineous marriage are again high, but they now stem not from a concern for Levitical Law but from the powerful tool consanguinity affords in an appraisal of the relative importance of mutation versus selection in maintaining the genetic burden of a population. Clearly the value of this tool is directly proportional to the quality and quantity of data available.

Recently, numerous studies have been published relating inbreeding to infantile and juvenile mortality. Notable among these are the studies of Sutter and Tabah (summarized in Sutter, 1958) in France, of Böök (1957) in Sweden, of Slatis, Reis, and Hoene (1958) in the United States, of Freire-Maia (1961) in Brazil, of Zerbin-Rüdin (1960) in Germany, and of a number of workers including ourselves in Japan. These studies differ markedly in size, scope, and design. In all, save our own, the mortality data are essentially retrospective in character. Experiences such as those with rubella in pregnancy should make us acutely aware of the possible biased nature of such observations. Be this as it may, it is the purpose of this paper to present the results of a continuing, anterospective investigation of the effects of inbreeding on mortality in Japan.

The Data

In the course of a study on the genetic effects of the atomic bombs in Hiroshima and Nagasaki, some 73,362 registered children were examined in these two cities between 1948 and 1953. Of this sample, 4,598 children were born to parents who reported a consanguineous marriage at the time of pregnancy registration and had received no or inappreciable amounts

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of radiation. The morbidity and mortality findings in these children at birth and, in a subsample, at 9 months of age, as contrasted to the remainder, have already been described (Schull, 1958). These findings were sufficiently provocative to indicate the need for further studies. Between 1958 and 1960, comprehensive follow-up studies were undertaken on these children of consanguineous marriages and a suitable control group. The nature of these follow-up studies has been described elsewhere (Schull and Neel, 1961). In all, 9,384 children, approximately half of whom were of consanguineous parentage, were selected for re-examination. Of this number, 275 were stillborn and are not considered here. An additional 145 were born to parents either more closely related than first cousins or more distantly related than second; these children, too, are not included in the data to be presented. For the remainder, through direct contact with the family or through the use of the *koseki*, the family household record required by law in Japan, it has been possible to ascertain, with few exceptions, whether these children were alive in 1958-1960, and if not alive, the date and age at death.

In Table 1, we present the distributions of children, alive and dead, by consanguinity, city, and present whereabouts of the family. The latter distinction, which will not be retained in subsequent tables, is given solely to indicate the errors which can arise through failure to take account of the possible non-randomness of the migrant population drawn from a city or district. In neither city is the death rate in the category " family moved from city " equal to that in the group " family living in city ", nor is the relationship of the former to the latter the same in the two cities. Be this as it may, the *koseki* renders this distinction unimportant in Japan. That this is so is indicated by the following observations; among 684 families who had moved from Hiroshima and where a *koseki* check to ascertain the status of the child was deemed necessary, in only 13 instances was a check not possible. In Nagasaki, of 834 cases similar to those in Hiroshima, in only 23 instances was a *koseki* check impossible. We turn now to the observations in Table 1.

The difference in over-all mortality between the two cities is not significant ($\chi^2=0.776$, DF=1), and the small difference observed is easily explicable in the somewhat longer period (six months on the average) of risk of death for children born in Nagasaki. Of greater interest is the apparent difference in the cities with respect to the effect of inbreeding on mortality. A weighted linear regression fitted to the data in Hiroshima removes a significant amount of variation; this is not true, however, in Nagasaki. Table 4 reveals significant heterogeneity between the cities. Is this heterogeneity evidence of dissimilar effects of inbreeding or is it explicable in terms of concomitant variation? Several lines of evidence are of importance here. Firstly, we note that exclusion of the non-inbred group would not materially affect the regression coefficients. Thus we are obliged to assume that if concomitant variation is the cause it is roughly distributed as F. This is an unattractive assumption and can, as a matter of fact, be shown to be at variance with the data, at least with respect to such measures of socio-economic status as " mats per person " (obtained by dividing the total number of standard-sized

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Tab. 1. The distribution of liveborn children, now alive or dead, by consanguinity, city, and present whereabouts of the family

Location of family	Parental relationship				Total
	Unrelated	Second Cousins	1-1/2 Cousins	First Cousins	
Hiroshima					
Family living in city					
Child alive	1444	276	253	676	2649
Child dead	98	28	26	76	228
Total	1542	304	279	752	2877
Family moved from city					
Child alive	357	70	67	161	655
Child dead	25	2	1	9	37
Total	382	72	68	170	692
Unable to locate family					
Child alive (?)	6	2	4	6	18
Child dead	1	—	—	—	1
Total	7	2	4	6	19
Total *					
Child alive	1801	346	320	837	3304
Child dead	123	30	27	85	265
Total	1924	376	347	922	3569
Nagasaki					
Family living in city					
Child alive	2172	453	386	1163	4174
Child dead	173	51	19	110	353
Total	2345	504	405	1273	4527
Family moved from city					
Child alive	406	80	54	218	758
Child dead	41	6	3	22	72
Total	447	86	57	240	830
Total					
Child alive	2578	533	440	1381	4932
Child dead	214	57	22	132	425
Total	2792	590	462	1513	5357

* Exclusive of " unable to locate ".

straw mats on the floor of the house by the number of persons residing in the house) and monthly expenditures on food per person in the household. Neither of these variables is significantly associated with degree of inbreeding in either city. It is worth pointing out that " mats per person " is also a measure of density of individuals within the house. Since density will be correlated with exposure to infectious disease on the part of the children, we may argue that the exposure factor must be roughly comparable within the consanguinity groups. This is an important consideration for infectious diseases are, collectively, a major cause of death in the age range here at risk.

It is conceivable that the variation between cities in inbreeding depression reflects a temporal heterogeneity. To test this hypothesis we have explored, within each city, the consistency of the effect of inbreeding from year-to-year. In Table 2 we give the distribution of deaths by year of birth of child by parental relationship and city. The analysis of these data is summarized in Table 5. It will noted that each city is consistent within itself in either suggesting an inbreeding depression, as in Hiroshima, or failing to do so, as in Nagasaki. The city differences cannot be explained, then, on the basis of a disproportionate contribution from a year atypical with respect to the magnitude of the inbreeding depression.

Still another source of heterogeneity may be examined. It may be argued that the analysis hereto presented would not reveal a situation in which the inbreeding depression occurred,

Tab. 2. Distribution of deaths by year of birth of child, parental relationship, and city. In parentheses is given the per cent mortality; births are livebirths only

Year	Parental relationship								Total births deaths	
	Unrelated births	deaths	Second cousins births	deaths	1-1/2 cousins births	deaths	First cousins births	deaths		
Hiroshima										
1948	226	17 (7.52)	42	4 (9.52)	41	5 (12.20)	112	12 (10.71)	421	38 (9.03)
1949	448	33 (7.37)	86	7 (8.14)	72	8 (11.11)	196	19 (9.69)	802	67 (8.35)
1950	368	35 (9.51)	65	1 (1.54)	75	6 (8.00)	207	20 (9.66)	715	62 (8.67)
1951	329	12 (3.65)	72	7 (9.72)	56	2 (3.57)	170	12 (7.06)	627	33 (5.26)
1952	292	18 (6.16)	59	5 (8.47)	48	3 (6.25)	130	10 (7.69)	529	36 (6.81)
1953	258	8 (3.10)	52	6 (11.54)	55	3 (5.45)	102	12 (11.76)	467	29 (6.21)
1954	3	—	—	—	—	—	5	—	8	—
Total	1,924	123 (6.39)	376	30 (7.98)	347	27 (7.78)	922	85 (9.22)	3,569	265 (7.43)
Nagasaki										
1948	57	12 (21.05)	15	2 (13.33)	12	1 (8.33)	33	6 (18.18)	117	21 (17.95)
1949	687	61 (8.88)	146	21 (14.38)	103	5 (4.85)	389	37 (9.51)	1,325	124 (9.36)
1950	584	55 (9.42)	133	12 (9.02)	101	10 (10.78)	337	28 (8.31)	1,155	105 (9.09)
1951	544	41 (7.54)	109	17 (15.60)	90	5 (5.56)	275	28 (10.18)	1,018	91 (8.94)
1952	494	23 (4.66)	103	5 (4.85)	97	—	291	17 (5.84)	985	45 (4.57)
1953	421	22 (5.23)	84	—	57	1 (1.75)	188	16 (8.51)	750	39 (5.20)
1954	5	—	—	—	2	—	—	—	7	—
Total	2,792	214 (7.66)	590	57 (9.66)	462	22 (4.76)	1,513	132 (8.72)	5,357	425 (7.93)

to a disproportionate degree, at one or a few ages. We may examine this hypothesis by distributing the data by age at death of the child. Table 3 sets out the distribution of infantile and childhood deaths by parental relationship and city. Again, we note that an inbreeding effect occurs both before and after the first year of life in Hiroshima, but not in Nagasaki. Along these same lines, it may be argued that a confounding of stillbirths with neonatal deaths might account for the differences between the cities. This seems unlikely, however, for the frequency of stillborn infants is almost identical in the two cities (1.38 per 100 births in Hiroshima and 1.47 per 100 in Nagasaki; see Schull, 1958), and, moreover, again an inbreeding depression is evident in Hiroshima but not in Nagasaki which is contrary to what would be needed to account for the present city difference.

Could systematic under-reporting account for the differences? The routine use of the *koseki*, and the recognized accuracy of the latter in recording fact of death makes it seem highly unlikely that substantial under-reporting could have occurred. Another line of evidence which suggests that under-reporting is unlikely comes from a comparison of the death rates in these data with those officially recognized for Japan. In Table 7, we present the death rates in Japan as reported in the Eighth (1947) and Ninth (1955) Life Tables. The Ninth Life Table was com-

Tab. 3. Distribution of infantile and childhood deaths by parental relationship and city as ascertained by the Child Health Survey. In parentheses is given the per cent mortality based upon the number of children at risk of death, exclusive of the " unknowns "

Status at Child Health Survey examination	Parental relationship				Total
	Unrelated	Second Cousins	1-1/2 Cousins	First Cousins	
			Hiroshima		
Died in first year of life	87 (4.52)	20 (5.32)	15 (4.32)	58 (6.29)	180 (5.04)
Died after first year but prior to Child Health Survey	33 (1.72)	10 (2.66)	10 (2.88)	26 (2.82)	79 (2.34)
Unknown	3		2	1	6
Alive at survey	1,801	346	320	837	3,304
Total	1,924	376	347	922	3,569
			Nagasaki		
Died in first year of life	144 (5.16)	43 (7.29)	8 (1.73)	101 (6.68)	297 (5.54)
Died after first year but prior to Child Health Survey	70 (2.51)	14 (2.37)	14 (3.03)	31 (2.05)	128 (2.53)
Alive at survey	2,578	533	440	1,381	4,932
Total	2,792	590	462	1,513	5,357

puted on the basis of the 1950 census population, and on vital statistics for the period October 1, 1950 to September 30, 1952. Though the Ninth Life Table may offer a satisfactory approximation to the present data, it is clear that neither the Eighth nor the Ninth Life Tables are precisely applicable. We note that the death rates in these data are lower than those in the Ninth Life Tables, and of course in the Eighth, but the difference would seem readily explicable in terms of the steadily declining infant and childhood mortality in Japan (as is evident in a comparison of the Eighth and Ninth Life Tables). Again, then, there is little basis for suspecting under-reporting.

The final possible cause of the apparent difference in inbreeding effects in the two cities to be considered is a systematic difference between the consanguineous parents in the two

Tab. 4. Analysis of the variation between cities in degree of inbreeding depression

Source of Variation	X^2	DF	P
Individual regressions			
Hiroshima	6.636	1	.01 - .001
Nagasaki	0.623	1	.25 - .50
Sum	7.259	2	.02 - .05
Common regression	2.039	1	.10 - .25
Heterogeneity	5.220	1	.01 - .02
Residual	10.616	4	.02 - .05
Total (Within cities)	17.875	6	.01 - .001

cities. We know that for both cities there are small although statistically significant differences between consanguineous and non-consanguineous parents as regards age and parity, but these differences are not of a magnitude to influence the findings in more than a minor way. Moreover, they are essentially the same for the two cities and hence not the basis for the intercity differences.

An Analysis of Cause of Death

What light does cause of death shed on this heterogeneity? Information pertinent to the cause of death among these children was available from one or more of four sources. Firstly, in Hiroshima but not in Nagasaki the death certificates on record with the Hōkensho (Public Health Department) were inspected and the cause of death recorded. These certificates appear to be no more, but probably no less, reliable than death certificates in most countries of the world. We judge them to be sufficiently accurate to permit the assignment of the deceased children to broad classes of causes. Secondly, there was available the mother's statement of cause of death. Thirdly, there were available the results of the clinical examinations of the child shortly after birth and, in some but not all instances, at 9 months of age. Finally, there were for a small fraction the results of autopsies performed at the Atomic Bomb Casualty Commission. For the present purposes, a child was said to have died of prematurity if the

birthweight was less than 2,500 grams and death occurred in the first month post-partum. In point of fact, the vast majority of deaths ascribed to prematurity occurred in the first week of life. The category " unknown " encompasses two groups, namely, those deaths where no data exist with regard to the cause of death, and those deaths where the cause is known but the etiology of the cause is not. The former constitute the bulk of the " unknowns ". " Com-

Tab. 5. Analysis of the within city variation by year in inbreeding depression

Source of Variation	X^2	DF	P
	Hiroshima		
Individual years	11.800	6	.05 - .10
Common regression	1.340	1	.10 - .25
Heterogeneity	10.460	5	.05 - .10
Residual	15.200	12	.10 - .20
Total	27.000	18	.05 - .10
	Nagasaki		
Individual years	3.154	6	.75 - .90
Common regression	0.182	1	.50 - .75
Heterogeneity	2.972	5	.50 - .75
Residual	30.735	12	.001- .01
Total	33.707	18	.01 - .02

binations " refer to deaths attributable to two or more causes. " Birth accidents " include primarily birth injuries.

The distribution of deaths by city by broad classes of causes is given in Table 6. Inspection of these data suggests that the consanguinity effect in Hiroshima is manifested primarily in an increased occurrence of death from infectious diseases and prematurity. The Nagasaki data are, again, at variance with these conclusions. There is no apparent effect of prematurity, and though deaths ascribable to infectious diseases appear to be more frequent among the children of related parents, there emerges no clear correlation with F, the coefficient of inbreeding.

Discussion

Morton (1961) has recently attempted to attribute the relative lack of an inbreeding effect in Nagasaki, and a similar relatively low effect in Kure, another Japanese city in which we have collected data, to " some environmental disturbance ". The foregoing analysis lends no support to this explanation; in our opinion the findings for Nagasaki are as valid as for Hiroshima, although the heterogeneity in the data from the former city is admittedly troublesome. Furthermore, as brought out in the first paper of this Symposium, other studies are now also

Tab. 6. Distribution of deaths by cause, city, and parental relationship. In parentheses, as per cent, are given the frequencies of the various causes

Cause of death	Parental relationship				Total
	Unrelated	Second Cousins	1-1/2 Cousins	First Cousins	
			Hiroshima		
Accident	12 (0.62)	3 (0.80)	2 (0.58)	6 (0.65)	23
Birth accident	1 (0.05)	—	—	2 (0.22)	3
Congenital defect	8 (0.42)	—	—	6 (0.65)	14
Infectious	39 (2.03)	9 (2.39)	12 (3.46)	28 (3.04)	88
Neoplasia	—	—	—	2 (0.22)	2
Prematurity	25 (1.30)	7 (1.86)	6 (1.73)	19 (2.06)	57
Combinations	3 (0.16)	2 (0.53)	1 (0.29)	2 (0.22)	8
Unknown	35 (1.82)	9 (2.39)	6 (1.73)	20 (2.17)	70
Total	123	30	27	85	265
			Nagasaki		
Accident	10 (0.36)	1 (0.17)	1 (0.22)	3 (0.20)	15
Birth accident	1 (0.04)	—	—	—	1
Congenital defect	12 (0.43)	1 (0.17)	1 (0.22)	8 (0.53)	22
Infectious	86 (3.08)	26 (4.41)	12 (2.60)	53 (3.50)	177
Neoplasia	2 (0.07)	—	—	—	2
Prematurity	38 (1.36)	8 (1.36)	1 (0.22)	20 (1.32)	67
Combinations	—	1 (0.17)	2 (0.43)	2 (0.13)	5
Unknown	64 (2.29)	19 (3.22)	7 (1.52)	46 (3.04)	136
Total	213	56	24	132	425

yielding relatively low inbreeding effects; it will be difficult to dismiss all those studies which fail to demonstrate a pronounced effect of inbreeding on mortality as the result of some environmental disturbance.

A clue as to the basis for the differences between Hiroshima and Nagasaki may be found in the results of the studies on morbidity which comprised the major aspect of this investigation. These studies, the results of which cannot be presented in any detail here, revealed significantly more children with major handicaps in the offspring of cousin marriages in Naga-

saki than in Hiroshima, with a consistent regression on degree of consanguinity. The combined impact of both serious morbidity and mortality in relation to consanguinity is quite similar for the two cities, as is shown in Table 8.

Of the various explanations for this finding, the most obvious, although not necessarily the most correct, is that there are significant genetic differences between the populations of Hiroshima and Nagasaki, such that although population frequencies for deleterious genes are

Tab. 7. A comparison of the death rates in these data with those reported in the 8-th and 9-th Life Tables of Japan. The entries are unweighted averages of the probabilities of death for males and females

Cumulative probability of death	Eighth Life Tables	Ninth Life Tables	These data
in 1 year	0.0813	0.0532	0.0533
2	0.1141	0.0648	0.0614
3	0.1332	0.0736	0.0664
4	0.1441	0.0802	0.0700
5	0.1510	0.0847	0.0724
6	0.1560	0.0877	0.0755
7	0.1597	0.0899	0.0776
8	0.1626	0.0915	0.0788
9	0.1650	0.0929	0.0831
10	0.1671	0.0940	0.0929

not greatly dissimilar for the two cities, these deleterious genes more often lead to death in Hiroshima than Nagasaki. The origin of these differences is probably not to be sought so much in the greater contacts of Nagasaki with the Western World as in the manner in which the Japanese Islands were peopled.

We now turn briefly to the interpretation of these data. They obviously have implications as regards the relative importance of " mutational " as contrasted to " segregational " loads in the etiology of genetically determined causes of death. A convenient way to approach this problem is through the computation of the ratio of the " inbred load " to the " randomly mating load ", the B/A ratios of Morton, Crow, and Muller (1956). In Hiroshima, this ratio, for mortality and serious morbidity combined, is 5.5, while in Nagasaki it is 5.0. Crow (1958) has pointed out that in the situation where two alleles are maintained at a locus entirely as a result of balanced polymorphism, the ratio of the inbred to random load is expected to be 2. If there are multiple alleles at the locus, and if all the heterozygotes are equal to each other and superior to any homozygote, the ratio of the first to the second of these two loads is equal to the number of alleles. If the heterozygotes are not all equal in fitness, the ratio will be less than the number of alleles. What does a B/A ratio of 5.0 indicate?

We can certainly agree at the outset of any attempt at the interpretation of such ratios that mutation produces rare recessive genes which are deleterious in the homozygote and at best neutral but possibly also deleterious in the heterozygote. Some portion of the inbreeding load is obviously due to such genes. It is an interesting thought that if approximately half the inbreeding load were due to such genes, for which the true B/A ratio was 20 — actually a rather

Tab. 8. The total mortality and morbidity among the liveborn children of consanguineous marriage in Hiroshima and Nagasaki. The cohort used as a base of reference are children defined by the methods of selection described in the text whose parents still reside in the two study cities. A deceased child appears only in the mortality entry and is not scored for major defect. The denominator for computing morbidity is total cohort number rather than number examined in the clinic. The resulting percentage estimate is biased downward by the inclusion in the denominator of the relatively few children who refused examination

	Hiroshima: parents related as				Nagasaki: parents related as			
	Unrelated	Second cousins	First cousins once removed	First cousins	Unrelated	Second cousins	First cousins once removed	First cousins
Total birth to parents still residing in the city	1542	306	277	752	2342	504	405	1276
Deaths among these births	98	30	24	76	170	51	19	113
% deaths	6.4	9.8	8.7	10.1	7.3	10.1	4.7	8.9
Total children examined in the cities	1409	267	248	665	2161	452	385	1152
Defective children	115	22	23	64	187	43	42	147
% defective children	8.2	8.2	9.3	9.6	8.7	9.5	10.9	12.8
Total known deaths plus defects	213	52	47	140	357	94	61	260
Estimated total mortality plus major morbidity	13.8	17.0	17.0	18.6	15.2	18.7	15.1	20.4

conservative figure (cf. Morton, 1961) — then the B/A ratio for the remainder need be only 2:1 to approximate the observed figures. These latter values would appear to be fully consistent with segregational loads. We would like to emphasize that we are not seriously advancing this possibility as a definitive interpretation — the situation is much too complex for so simple an approach — but only as an illustration of some interpretative possibilities.

If we may be permitted the working hypothesis that segregational loads are of considerable importance in genetically determined death, it is appropriate to inquire how these loads become manifest. Elsewhere one of us has suggested that a significant proportion of congenital defect — which affects some 10% of all zygotes — may reflect the operation of homeostatic genetic systems of the type particularly discussed by Lerner (1954), a suggestion we wish to reiterate at this time. This suggestion has recently been vigorously challenged by Morton (1960). With respect to the actual " evidence " quoted by Morton as indicating homeostatic systems are not likely to be important in the etiology of congenital defect, time does not permit the complete reply which will shortly be forthcoming. Suffice it to say here that inferences drawn from the study of muscular dystrophy, deaf-mutism, and mental deficiency, phenotypes already known to result in a high proportion of cases from simple recessive inheritance, phenotypes having frequencies consistent with mutation pressures, and phenotypes selected for study for that very reason (cf. Crow, in press) are scarcely apt to be critical. The relative importance of mutational as versus segregational genetic loads in man will only be settled by the patient accumulation of the necessary observations, including particularly efforts to relate the many genetic polymorphisms now recognized to biological phenomena — including congenital defects.

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