95. *Recent Studies of Human Genetics in Japan. I*

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Human genetics has of late advanced rapidly in the knowledge of the biochemical, serological, morphological, and cytological basis of hereditary diseases. There has also been steady improvement in statistics and epidemiological technique applied to problems in human population genetics.

To these advancements in Japan, several pioneers of human genetics contributed from different fields and standpoints. However, they were obliged to devote only a fraction of their time to human genetics, because there had been no human geneticist assigned as full-time staff in universities and institutions of Japan until the Department of Human Genetics, Tokyo Medical and Dental University, was established in 1956.

The advances of the last three decades in diagnosis and therapy, the more widespread dissemination of public health information and the governmental activities in the area of preventive medical and public health services, have markedly reduced the number of deaths from infectious and contagious diseases. In Japan, for instance, the proportion of deaths attributable to such diseases is, at present, only 1/6 of those in 1930; while the number of deaths attributable to genetic and/or constitutional diseases have remained unchanged (see Table I).

This fact has led many doctors in the fields of clinical and general medical sciences to pay an increasing attention to human genetics. Moreover, individuals with genetic or constitutional disease and the parents of such persons have been seeking for the etiology of their condition and the genetic prognosis for their diseases. Thus many physicians find in their practices that they are required to explain the genetic basis of the disease of their patients, particularly is this true in the university hospitals and other big hospitals.

The unfortunate events of the exposure to the atomic bombs have also led Japanese people to consider the genetic effects of radiation in man.

Under these recent circumstances, several physicians and geneticists were assigned as full-time staff in some national institutions.

Consanguinity study. The frequency of consanguineous marriages

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Table I. Change of specified death rate (per 100,000)

	1941	1957	%
Total number of death	2,279.4	826.1	36.24
Infectious diseases			
Tuberculosis	213.0	46.9	22.02
G. I. Infection	272.9	25.7	9.42
Pneumonia and bronchitis	292.9	59.2	20.21
Dysentery	14.6	4.1	28.08
Typhoid	22.6	0.1	0.44
Diphtheria	6.9	1.0	14.49
Measles	24.8	3.0	12.10
Whooping cough	12.4	0.4	3.23
Total	895.5	140.4	16.34
Genetic and constitutional diseases			
Cerebral hemorrhage	160.7	151.7	94.40
Malignant neoplasm	71.9	91.3	126.98
Cardiac diseases	66.4	73.1	110.09
Diabetes	3.2	3.0	93.75
Congenital malformation	304.5	323.5	106.24
Total	606.7	642.6	105.92

in Japan has been extensively investigated. There are, however, relatively few exact data to estimate the effects of consanguineous marriages.

If the materials are obtained more exactly by reliable technique in statistical view, these materials will contribute to estimate the burden of deleterious genes. Moreover, these will lead us to more basic knowledge on genetic structure of human population and will contribute to estimate the genetic effects of radiation, too.

A) Epidemiological survey in Shizuoka.¹⁾⁻³⁾ For these purposes, a relatively large group of investigators (Chairman: Dr. Taku Komai) was organized by the Genetic Committee of the Science Council of Japan in 1957. This project related very closely in cooperating the progress of research program and in exchanging materials with the Child Health Survey organized by J. V. Neel and W. J. Schull, University of Michigan. The actual researches have been arranged to be very similar in the nature for the purpose of comparing the both outcomes. Uniqueness of this research in Shizuoka is the estimation of consanguinity level. The family registration (*Koseki*) is very helpful to estimate the exact relationship of parents. More than 10,000 school children of 6,544 families were observed in 1958-1960.

Anthropometric, psychometric, medical, and dental examinations have been done by specialists of these fields. Also, by means of home visit, several biological information, socio-economical status, maternal reproductive history, and brief medical history of children

have been obtained.

At present, obtained materials are ready to be analysed but still premature to show any evaluation of this study. However, a part of the material will give us more reliable data than those of previous studies because of "*Koseki*" record check.

First preliminary report will be presented to the Medical Genetics Symposium, as a part of the Pacific Science Congress, Hawaii, this August.

B) Genetic study of isolated population.¹⁾⁻³⁾ Generally, the frequency of consanguineous marriage in Japan is higher than that in western countries. As a part of the above-mentioned research program, four research groups have been carrying on the investigations on the inhabitants of four different areas. The major interests of these surveys are centered in estimating the coefficient of inbreeding, incidences of blood groups and several normal characters, prenatal and post-natal mortality, incidence of hereditary abnormalities, and so on.

In these studies, for the purpose of estimation of consanguinity effects, a big task to consider the background responsible to constitution of the inhabitants in these areas might be strongly requested.

Regarding the estimation of the exact and detailed blood relationship among inhabitants, several investigators are attempting to obtain the historical materials which will make sure the relationships.

According to a preliminary analysis, different mortality was observed in several areas.

C) Theoretical and other basic studies. The most recent development in this area was the demonstration by Morton, Crow, and Muller (1956)⁴⁾ and Kimura (1958)⁵⁾ of means by which one can estimate the burden of deleterious genes from data on inbred individuals. Both studies are considering theoretical approaches for this purpose and estimating the burden of deleterious genes.

Estimation of consanguinity level among parents and identification of exact relationship are most important basic procedure in this type of study. For these purposes, K. Ohkura (1960),⁶⁾ and K. Ohkura and I. Komatsu (1961)⁷⁾ have emphasized the advantage of use of the "*Koseki*" record (the Family Registration) in the study of human genetics, and they revealed several methods to find the relationship among individuals by the data from "*Koseki*" records. These may be more simplified and efficient methods than others.

K. Ito and other members of the Shizuoka study group are attempting to find efficient mathematical and statistical techniques to show the effects of consanguinity from data obtained from Shizuoka. Some highly qualified methods will be requested in the analysis of these materials.

Studies on specific diseases and anomalies. A) Acatalasemia. Shigeo Takahara,⁸⁾ Okayama University, has found a rare and distinct trait characterized by lack of catalase activity in blood with frequent complication of oral gangrene, then he and his collaborators attempted to find the etiology of this trait for last 10 years. At present, the following results are obtained:

1. This trait is due to simple recessive gene, and almost all of the affectives are offspring of consanguineous marriages.

2. Carrier state can be shown very precisely in the level of catalase activity. Nishimura et al. (1959)⁹⁾ have shown that the level of catalase activity in heterozygotes of this gene is about intermediate between that of affected (no activity) and that of normal individuals.

3. So far, the trait is found only in Japanese and Korean.

4. The gene frequency is very different in areas.

5. Very recently, Takahara and the collaborators confirmed that no catalase protein was found in the blood of affected individuals.

B) Deaf. Toshiyuki Furusho¹⁰⁾ has examined institutionalized deaf children in Kyushu district including 1,561 congenital cases in 1,042 families, as well as 1,042 non-congenital cases. Some 33.11% of the affectives with congenital deaf were born to consanguineous parents, while in case of non-congenital deafs 6.77% were born to consanguineous parents. His result is suggesting that the majority of congenital deaf is due to a recessive autosomal gene, and there is possibility of existence of some other gene or genes to be responsible for the cause of this abnormality. The frequency of the major gene was estimated as 0.0106. He is examining another about 3,000 deafs who registered to City Halls in Ibaragi, Tochigi, and Gumma prefectures.³⁾ About a half of them and their relatives have been examined. The study will bring us the genetic aspects of congenital deafness in Japan.

C) Harelip and cleft palate. The frequency of occurrence of harelip and cleft palate of Japanese is twice as high as that of Caucasian, that is, about 1 in 500.

Y. Kobayashi (1958)¹¹⁾ has made a genetic and clinical study of these anomalies using the data obtained from the Red Cross Hospital and Tokyo Medical and Dental University in Tokyo. The incidence was found to be 0.21%. He found some interesting result in sex ratio of the affected which contrasted to that of Caucasian. That is, 1:1 in infants with harelip alone, while remarkably excess number of male was reported on Caucasians. Besides, excess number of male in case of harelip with cleft palate and excess number of female in case of cleft palate alone were found.

From his family data, he concluded that the cleft palate alone and harelip with or without cleft palate might differ in their etiology. There exist some common factors responsible for both anomalies; if some independent factors act in a particular stage of development, harelip with or without cleft palate will occur, and simple cleft palate may occur with existence of other independent factors. Rate of consanguineous marriages among the parents of affected individuals is not higher than the average.

S. Takahara, S. Kurozumi, and K. Ohkura¹²⁾ have made a large scale family follow-up study of harelip and cleft palate. Some 350 families of propositus who were administrated to Okayama University Hospital for the purpose of medical care for these abnormalities since 1916 were examined in 1960. The major interest of this survey was divided into two, that is, the estimation of empirical risk of recurrence of these abnormalities, and the follow-up study of the rehabilitation of the treated propositus. The empirical risk of recurrence of these abnormalities was estimated as 1.73% when the parents were normal, namely, 16 affectives were found in 922 siblings of propositus. The incidence of affectives in offspring of propositus was 3 in 118, in offspring of non-propositus affectives was 8 in 57.

D) Pelger's nuclear anomaly. Y. Handa and his collaborators found 21 cases of this anomaly in 30,530 school children in Wakayama.¹³⁾ The incidence (0.069%) is somewhat lower than that in Berlin (0.1%) and higher than that in London (0.016%). 20 of propositus were born to affected parents and 1 case had non-affected parents. This is probably a new mutant.

Table II

	Number	Parental consanguinity	
		1st cousin (%)	Total (%)
Albino	106	41.5	66.6
Corneal disease	1,422	13.3	18.3
Congenital	314	26.3	35.4
Postnatal	1,108	9.6	13.5
Cataract	1,137	18.2	26.2
Congenital	865	22.0	31.4
Postnatal	272	6.3	9.4
Retinitis pigmentosa	434	39.1	48.5
Nystagmus	135	46.5	56.2
Optic atrophy	719	17.7	24.9
Congenital	424	28.0	36.0
Postnatal	295	5.7	9.1

E) Study of blind individuals. A. Nakajima¹⁴⁾ collected data on causes of blindness from about 8,000 institutionalized individuals in about 100 institutions. According to his preliminary analysis, some

distinct effects of inbreeding were revealed in several diseases (Table II).

Concerning the heterogeneity of ophthalmic disorders, C. Kobayashi (1959)¹⁵⁾ revealed 3 different modes of inheritance in retinitis pigmentosa and 2 different modes were revealed on congenital cataract by A. Nakajima.

F) Phenylketonuria. K. Tanaka and others¹⁶⁾ have examined 5,419 institutionalized mental defectives in 111 institutions all over Japan. 9 were found to be phenylketonuric with 0.166% of incidence.

The segregation ratio was estimated as $11.90 \pm 4.54\%$ when used living children alone, $15.91 \pm 5.51\%$ —when included possibly affected and dead sibs, and $14.00 \pm 4.91\%$ —when all dead sibs were included. These figures are certainly lower than 25% as expectation of simple recessive inheritance.

References

- 1) Ann. Rep. Min. Educ. Radiation—Coope. Res. no. 7, 43-50 (1958).
- 2) Ibid. Radiation—Coope. Res. no. 13, 43-51 (1959).
- 3) Ibid. Radiation—Coope. Res. no. 13, 45-52 (1960).
- 4) Morton, N. E., Crow, J. F., and Muller, H. J.,: Proc. Nat. Acad. Sci., **42**, 855-863 (1956).
- 5) Kimura, M.,: Jap. Jour. Human Genet., **3**, 51-70 (1958).
- 6) Ohkura, K.,: Jap. Jour. Human Genet., **5**, 61-98 (1960).
- 7) Ohkura, K., and Komatsu, I.,: In press.
- 8) Takahara, S.,: Lancet Dec. 1952, p. 1101.
- 9) Nishimura, E. T., et al.: Science, **130**, 333-334 (1959).
- 10) Furusho, T.,: Genetic study of congenital deafness, Jap. Jour. Human Genet., **2**, 35-58 (1958).
- 11) Kobayashi, Y.,: Jap. Jour. Human Genet., **3**, 73-107 (1958).
- 12) Takahara, S., et al.: In press.
- 13) Handa, K.,: Wakayama Med. Jour., **12**, 759-767 (1960).
- 14) Nakajima, A.,: Rinsho Ganka (Clinical Ophthalmology), **14**, 1757-1761 (1960).
- 15) Kobayashi, C.,: Jour. Jap. Ophthalmol. Soc., **63**, 3839-3859 (1959).
- 16) Tanaka, K., et al.: To be published.