APPENDIX NO. 6

THE QUESTION OF THE GENETIC EFFECTS OF THE ATOMIC BOMBING

by

James V. Neel

1st Lt., M.C., A.U.S.

THE QUESTION OF THE GENETIC EFFECTS OF THE ATOMIC BOMBING

Lt James V. Neel

INTRODUCTION:

The ability of irradiation of various types to accelerate the normal mutation rate in a wide variety of plant and animal species is a fundamental observation in radiobiology. With the present extensive background of information on this subject, an obvious question which arises in any consideration of the late effects of the atomic bombing is the genetic one. Have the various plant and animal species involved in the bombing, including man, received sufficient irradiation to effect a detectable increase in the mutation frequency?

JAPANESE PROGRAM:

The Japanese group has appreciated the significance of this question from the first. Their activities fall into two categories, namely, investigations of human material, a function of the Medical Section of the Japanese Special Committee and for the most part at present under the immediate supervision of Dr. Ikuzo Matsubayashi, and investigations of plant and animal material, primarily a function of the Biological Section and under the immediate supervision of Dr. Yoshiro Abe and Dr. M. Chino. Conferences were held with the three above-mentioned individuals, as well as with certain other investigators, to be mentioned below. The activities of some other sections of the Japanese Special Committee also have genetic implications.

The program of the Medical Group is as follows: An attempt to determine the results of all conceptions in the Hiroshima area is being organized. All pregnant women are required by government regulation to register in the early months of pregnancy, in order that they may obtain certain additional food and clothing allowances. Government regulations also require that the termination of any pregnancy after the third month be reported. Dead births, no matter what the age of the foetus, are to be registered on a form issued by the Ministry of Welfare. Live births, no matter what the age, are registered on a form issued by the Ministry of Justice. A limited amount of information of genetic value would be provided by this system of registration if it were functioning efficiently. The Japanese Medical Group studying atomic bomb survivors at Hiroshima has attempted to supplement this information by two additional measures. The first is a questionnaire, to be filled out by pregnant women at the time of registration. This questionnaire covers briefly the medical history of the prospective parents at the time of the bombing, and the reproductive history of the prospective mother; a translation of the questionnaire is available for examination. The second measure involves an attempt, at the termination of each of these pregnancies, whether prematurely by abortion, miscarriage, etc., or at term, to obtain information on the nature of the foetus or child. It is well known that abnormal foeti tend to be eliminated prior to term, thus necessitating

a careful check on abortion and miscarriages. This program has not yet gone into operation at Hiroshima, so that no data are available. As yet no similar program has been planned for Nagasaki.

The Japanese program proceeds along obvious lines and so far as it goes is soundly conceived. There are apparent, however, two serious defects. The first of these is the lack of suitable control studies. It is obvious that in this case the approach to the problem of genetic effects is the statistical one. A specific pathology in the next generation can never be attributed to the effects of the bomb, but if there is a definite increase in the occurrence of abnormal products of conception in irradiated persons, one may surmise that this is related to the bombing. One must therefore have control studies comparable in extent to those on irradiated persons. The Japanese had planned to use the vital statistics of the past some years as a partial control. This leads to a consideration of the second defect in the present scheme. It is the opinion of the Commission that there are serious inaccuracies in the present vital statistics returns in Japan. It is obvious from a study of the present statistics that only a portion of abortions and miscarriages is being reported. It also seems probable that the occurrence of certain congenital malformations in the new-born may be concealed by the practice of infanticide. Further, in the absence of premarital and neonatal serological tests for lues, the incidence and importance of this disease in the new born, and its role in the production of stillbirths, is poorly known.

CONTROL AREAS:

These defects in the Japanese program are at least in part remedial. The necessity of adequate control studies was appreciated by the Commission from the first, and from data available in Tokyo three areas were picked as possible control sites before the group departed on the survey tour. During the tour each of these sites was scrutinized as to similarities to Hiroshima and Nagasaki, and investigated regarding facilities for any studies that might be undertaken. These three areas were the cities of Osaka, Fukuoka, and Kure. After due consideration the latter was chosen as most suitable. It is comparable in size to Hiroshima, being located about 25 miles from the former. The city was heavily bombed during the war. From statistics furnished by Col. Howe of the Public Health and Welfare Section of SCAP, it would appear that the nutritional levels of Kure and Hiroshima are comparable, both being relatively poor. There is a Military Government Team in Kure, but none in Hiroshima. The proximity of the cities makes commuting between the two feasible, thus simplifying the necessary field of organization. Living quarters are available at Kure. Hospital facilities can be obtained in Kure at the Kure Mutual Relief Hospital, and tentative arrangements for such facilities have been made. A meeting has been held with the leading physicians and midwives of the city, and the possibility of using Kure for control studies on Hiroshima and Nagasaki presented. The initial steps have thus been taken to set up an adequate control area.

RELIABILITY:

The problem of improving the reliability of the vital statistics is more serious. It can be met in these areas to a certain extent by enlisting the aid of physicians, midwives, and the general public through eduction and directives. In this connection it should be pointed out that

85% of deliveries in Japan are by midwives. These steps, however, are not enough. Additional Japanese personnel must be obtained for these areas. This problem, of improving the quality of the vital statistics, is of importance to all Japan, a fact realized by SCAP shortly after the beginning of the occupation. At present a large-scale reorganization of the collection and tabulation of vital statistics in Japan is under way, under the general direction of Mr. L. V. Phelps in the Public Health and Welfare Section of SCAP. Numerous conferences have been held with him as to the most fruitful avenues of cooperation. A memorandum to Mr. Phelps on this subject is included in the appendix.

SPECIAL CONSIDERATION:

Certain genetical and practical considerations vital to the formulation of any program should be introduced at this point. It is convenient to distinguish between dominant and recessive genes, dominants finding phenotypic expression in the heterozygous state but recessives requiring the homozygous condition for their manifestation. Mutation resulting in dominant genes may be detected in the next generation, whereas mutation resulting in recessives may go undetected for many generations, unless the recessives happen to be sex-linked. Inasmuch as the majority of naturally occurring and irradiation-induced mutation in experimental material have proven to be recessives, it follows that only a fraction of any genetic change that may have been induced could be detected by the above-described methods. A program to detect the recessive mutations that may come to light two, four, or more generations hence appears impractical. What we are dealing with is not a laboratory experiment, but a situation which must be approached with due appreciation of the present conditions in Japan. Under the circumstances it is impossible to look beyond the next ten or twenty years, a fact which suggests that attention be concentrated on dominant and certain sex-linked recessive mutations. Furthermore, in view of the possibility of genial elimination of mutations associated with chromosomal aberrations, the program should be organized as rapidly as possible. On the other hand, the organization should be such that observations may be extended to the second, third, or later generations if that becomes feasible.

The survivors of the bombing will have received doses of irradiation ranging from negligible to just short of lethal. It is obviously impossible to say on a priori grounds whether a sufficient number of people will have absorbed sufficient irradiation to produce sufficient dominant mutation to result in a significant alteration of vital statistics. However, comparison of this situation with the known experimental facts suggests that the magnitude of the change, if detectable at all, will be small. Large scale studies utilizing all the available material and accurate vital statistics are thus necessary. Anything short of such an investigation can only yield equivocal results - although there is no guarantee that large scale work will not also yield equivocal findings. It is important to point out that there is a definite limit to the amount of clinical material available. For instance, it can be estimated that the number of survivors within the 2-km zone, where radiation sickness was common, is approximately 80,000 in Hiroshima, and 15,000 in Nagasaki. Many of these have since left the area. Let us assume that we confine our studies to these cities, without trying to locate those who left subsequent to the bombing, and that there are now

present in these cities some 50,000 of the survivors within the 2-km. ring. A mean birth rate of 25 per 1000 per year for the next 10 years provides a sample of only 12,500 births from "heavily irradiated" persons. However, it would be necessary to screen many persons to derive this sample. There is room for debate as to whether the effort which must be expended on such studies is justified by the possible scientific returns. However, in our interest in this as an experiment in radiobiology we should not lose sight of the public health aspects of this situation in an age of atomic energy. The latter may by themselves justify a considerable expenditure of effort, and failure to demonstrate a genetic effect of the bombing is fully as important as finding a measurable influence. In this connection it should also be pointed out that regardless of whether these studies reveal a genetic effect of the atomic bombing they will, if properly organized, yield much fundamental information on the genetic structure of the Japanese people.

PROPOSED PROGRAM:

In the light of the foregoing, it is felt that a program to detect possible genetic effects, if deemed desirable, can best proceed along the following lines:

1. Organize, in Hiroshima, Nagasaki, and a control area (Kure), a system of pregnancy registration that works, this to include the irradiation history of the parents.

2. Obtain as complete information as possible on the outcome of each registered pregnancy.

3. Follow up each report of an abnormal termination of pregnancy or a congenital malformation with detailed family studies.

4. Develop a system of checking on the completeness and accuracy of the records, such as requiring registration by both family and physician or midwife.

5. Conduct these studies on a sufficiently large scale that the results will have statistical significance.

6. Integrate this program with an improved and more accurate system of death certification, so that genetic effects not apparent at birth but detected subsequently may be recorded.

7. Put the program insofar as possible into competent Japanese hands, through the Japanese Government, with only enough American supervision and cooperation to facilitate a smoothly functioning program. This program at best will detect only a fraction of dominant mutations.

PARTICULAR CONSIDERATIONS:

Attention must be given to the problem of following persons who were in Hiroshima and Nagasaki at the time of the bombing and subsequently departed.

A question related to the problem of genetic effects is that of diminished fertility or sterility as a result of irradiation. It is suggested that the reproductive histories of several hundred women in the child bearing age who suffered from radiation sickness be compiled during the next ten years, for comparison with the reproductive histories of a comparable number of women who were in Hiroshima or Nagasaki at the time of the bombing but did not show the symptoms of radiation disease.

The assay of possible genetic effects is much more readily performed in plant and animal material than in man, with, however, the important qualification that in animal and, to a lesser extent, plant material, it is often impossible to be certain of position at the time of the bombing. The Japanese efforts to utilize animal material have been completely nullified by the chaotic conditions and poor food situation. Thus, in Hiroshima Dr. Yoshiro Abe of the University of Literature and Sciences had in the animal colony of the University at the time of the bombing 32 rabbits. The approximate distance of the colony from the hypocenter was 1.6 km. Eighteen died as a result of the bombing. It was planned to use the remaining 14 in breeding experiments. However, because of poor caging facilities and predators, some possibly human, half of the remainder were soon lost, and it was then necessary to sacrifice the few that were left because of food shortages. Dr. M. Chino and Dr. T. Komai of Kyoto Imperial University, both with an extensive experience in Drosophila genetics, undertook to collect Drosophila in the Hiroshima area and analyze their genetic composition, for comparison with other wild populations of flies. These experiments were soon abandoned because of lack of facilities, especially fly media, and lack of adequate testor stocks.

The work on plant material, insofar as we have been able to familiarize ourselves with it, has been hardly more profitable. Dr. Naomasi Shimotomai, of the University of Literature and Sciences of Hiroshima, and Dr. Hiromi Nakayama, of Tokyo Imperial University, have both studied the occurrence of variegation in plant leaves in the bombed areas, this variegation consisting of albino areas on otherwise green leaves. Variegation has been observed in a variety of plant species, and photographs illustrating this point are available for the Commission. However, there are no control observations as to the normal frequency of such variegation, and thus far no attempt to analyze the nature of the phenomenon. The complicated problems presented by variegation in plants are well recognized. It is not known in the present instance whether this variegation reflects a change in the plastids or in the nucleus of an early leaf bud. If it is due to a nuclear change, certain rather diverse possibilities have to be recognized, each of which requires some interesting assumptions. Albinism is almost invariably a recessive trait. In explanation of these spots one must therefore assume that two homologous loci were simultaneously affected, or that the plant was originally a heterozygote, and the normal locus affected, or that this is the very rare dominant albinism.

ANIMAL EXPERIMENTS:

If it seems desirable to initiate certain animal experiments, to parallel the work on man, then of the various plant and animal species that could be employed, the fruit fly, Drosophila, is most susceptible to

an exact genetic analysis. The disadvantage to work utilizing this organism is that in the ten or more fly generations which have elapsed since the bombing, there has undoubtedly been a great deal of migration, as well as elimination of dominant and, to a much lesser extent, recessive mutations by natural selection. If the genetic variability of flies collected in the bombed areas was found to be significantly greater than in several control areas, this could be construed as evidence for irradiation-induced changes in the genetic composition of these - and presumably other - organisms. However, a negative result would not mean that no such change would have occurred, since selection and migration might by now have rendered the effects of this insult to the germ plasm undetectable. The value of a Drosophila program is debatable.

If a Drosophila program is undertaken, it is suggested that it utilize flies collected at Nagasaki, the reason being that the total dose of irradiation received by organisms in this area was quite possibly greater than at comparable distances from the hypocenter in Hiroshima, and that the dose was distributed over a longer period of time.

OBSERVATION ON PLANT MATERIAL:

The Japanese have made a number of observations purporting to show that vegetables grown in Nagasaki from seed from plants that were well beyond the known radius of bomb effects tended to assume unusual forms when grown near the hypocenter. The most extensive of these observations to come to our attention were those by Dr. Takeo Furuno, formerly chief of the Agriculture Station of Nagasaki Prefecture, and at present director of a society for the better utilization of land by crops. He has maintained two experimental garden plots, one 150 meters from the hypocenter, and the other 500 meters from the hypocenter. Abnormal vegetative forms of Brassica chinensis, Lappa edulis, Cucurbita moschata, Solanum melongena, and other species are reported to be far more frequent in the plot nearest the hypocenter. A detailed report of these findings is on file. This is attributed to some effect of the atomic bombing on the soil. These two plots were inspected and specimens of the vegetables examined - it was the opinion that soil differences complicate the picture to an extent where it is impossible to reach conclusions.

DIFFICULTIES:

The difficulties of organizing along sound lines any genetic program, whether concerned with man, Drosophila, or plant material, are great. Unless through various channels a major effort can be organized, involving at a first estimate 15-25 Japanese personnel of various types, the results will be unsatisfactory and the effort largely wasted. The success of the effort is closely linked with the problem of improving Japanese vital statistics, and this in turn is closely related to the problem of improving the general level of medical practice in a country under severe post-war stress. These are problems whose roots go deep. If, on the other hand, such a large scale project can be set up, the scientific value almost inevitably will extend beyond the specific question of a genetic effect of the atomic bombing.