greatest depression was observed between the seventh and ninth months after exposure, and recovery, when possible, usually occurred by the end of the second year.

References

Collection of the Reports on the Investigation of the Atomic Bomb Casualties. 2 vol. 1953. Japan Society for the Promotion of Science. Tokyo: Maruzen.

Guskova, A. K., and G. D. Baysogolov. 1971. "Radiation Sickness in Man." Translation series, AEC-tr-7401.

Kajitani, T., and S. Hatano. 1953. "Medical Survey on Acute Effects of the Atomic Bomb in Hiroshima." In *Collection of the Reports of the Investigation of the Atomic Bomb Casualties,* vol. 1. Japan Society for the Promotion of Science. Tokyo: Maruzen.

Oughterson, A. W., G. V. LeRoy, A. A. Liebow, E. C. Hammon, H. L. Bernett, J. D. Rosenbaum, and B. A. Schneider. 1951. *Medical Effects of Atomic Bombs: The Report of the Joint Commission for the Investigation of the Atomic Bomb in Japan.* 6 vol. Washington, D.C.: U.S. Atomic Energy Commission.

Oughterson, A. W., and S. Warren, eds. 1956. *Medical Effects of the Atomic Bomb in Japan.* New York: McGraw-Hill.

Warren, S., and J. Z. Bowers. 1950. "The Acute Radiation Syndrome in Man." *Annals of Internal Medicine, 32*:207–216.

8

Delayed Medical Effects at Hiroshima and Nagasaki

Takeshi Ohkita, M.D.

Soon after the end of World War II, the Japanese and United States governments sent teams to investigate the effects of the Hiroshima and Nagasaki atomic bombs. Although it was known in 1945 that ionizing radiation could induce mutations, cancers, and other deleterious effects in plants and experimental animals, little was known about how ionizing radiation from atomic bombs might affect the exposed survivors in the succeeding years.

The Atomic Bomb Casualty Commission (ABCC) was organized in 1946 under the direction of the National Research Council of the National Academy of Sciences in the United States, and in 1948 the National Institute of Health of the Japanese Ministry of Health and Welfare formally joined in its studies. The Research Institute for Nuclear Medicine and Biology was started at Hiroshima University in 1961, and the Atomic Diseases Institute at Nagasaki University in 1962. In 1975, the ABCC was dissolved and the Radiation Effects Research Foundation (RERF) replaced it as a joint enterprise of the Japanese and American governments, to continue the surveillance of the Hiroshima and Nagasaki atomic bomb survivors for long-term aftereffects.

In this report, a brief summary will be presented on the major points based on careful and painstaking studies carried out by many American and Japanese scientists. Table 1 gives the

Table 1. Main studies on the aftereffects of the atomic bomb, Hiroshima and Nagasaki.

Keloids and overgrowth of scars	Malignant tumors
Blood disorders	Chromosome changes
Eye lesions	Genetic effects
Disturbances of reproductive function	Aging and life span
Effects on fetuses exposed in utero	Psychoneurological disorders
Growth and developmental disturbances	

major research studies made to date on the late effects of the atomic bomb.

Keloids and Overgrowth of Scars

After the healing of some very severe burns due to the radiant heat from the bombs in both Hiroshima and Nagasaki, overgrowth of scar tissue and keloids were frequently observed among those who were burned within 1.7 kilometers (1 mile) of the hypocenters. The incidence of keloids on various parts of the body in 1946–1947 varied between 20 and 50 percent for thermal burns studied. Formation of keloids occurred mostly on exposed parts of the body such as face, neck, and extremities. As keloids are physically deforming, are accompanied by stinging pain and itching, and are associated with functional disorders of the joints, survivors suffered both physically and mentally.

Surgeons in both Hiroshima and Nagasaki devoted a great deal of effort to the treatment of keloids, however, they often recurred after surgical removal or skin transplantation. Many keloids transformed to ordinary scars during the 10-year period following 1946 and 1947, the peak years for keloid formation.

Blood Disorders

After the bombing the blood cells of survivors were extensively investigated. These investigations have continued uninterrupted over the years. In most survivors, the blood cell values, which

Keloid formation on burned skin. This girl was exposed at about 1100 meters from the hypocenter in Hiroshima, July 1947. (Courtesy of Dr. T. Ohkita.)

frequently had significant abnormalities, returned to the normal range by the end of the second year. Delayed blood disorders, however, were more insidious and required careful study during the last 35 years for their possible cause-and-effect relationship to atomic exposure. These are summarized below:

- The incidence of leukemia among the atomic bomb survivors, which had increased significantly during the mid-1950's, has decreased steadily since then, but the leukemia risk in heavily exposed survivors, especially in Hiroshima, is still higher than the average value for Japan. No relationship has been demonstrated between the incidence of leukemia among children exposed in utero and nonexposed children born later to atomic bomb survivors.

A nurse taking a blood sample from this girl's ear. The girl has lost her hair, an early symptom of radiation syndrome. Nagasaki, early September 1945. (Yasuo Tomishige, Hiroshima–Nagasaki Publishing Committee.)

- The incidence of multiple myeloma has been found to be significantly elevated 20 years after the bombing in the heavily exposed survivors.
- The risk of developing malignant tumors in lymphoid tissue has been found to be linked to radiation dose, but the dose relationship is not conclusive.
- Cases of idiopathic myelofibrosis have been reported among atomic bomb survivors in autopsy subjects, but it is not possible to assert that this is due to radiation, because of the complexities of the disease pattern, the paucity of cases, and the inconclusiveness of the link between autopsy findings and exposure dose.
- The incidence of aplastic anemia and polycythemia vera has been shown clearly not to be related to atomic bomb exposure.

Eye Lesions

Following exposure to the atomic bomb, eye lesions were numerous and of three types: (1) lesions from direct injury (thermal burns especially of the eyelids; trauma due to foreign bodies, especially glass splinters; and flash lesions to the cornea, conjunctiva, and retina), (2) lesions from the effects of radiation illness, including those from anemia, hemorrhage, and infection, and (3) delayed effects, including cataracts and scar deformation.

Among the delayed effects, atomic bomb cataracts were the first

---

anaplastic carcinoma cancer in which there is loss of structural differentiation in cells.

aplastic anemia anemia caused by deficient production of red blood cells.

granulocytic leukemia leukemia of the white blood cells that contain granules.

idiopathic myelofibrosis replacement of the bone marrow by fibrous tissue; idiopathic means of unknown origin.

keloid scar formation characterized by irregular shape, raised sharply above the surrounding skin.

leukemia progressive malignant disease of the blood-forming organs characterized by a proliferation of white blood cells in the blood and bone marrow. In acute leukemia death occurs within a few months of the onset of symptoms; the duration of chronic leukemia exceeds one year, with a gradual onset of symptoms.

lymphocytic leukemia leukemia of the lymphocytes, white blood cells that do not contain granules and are formed in lymph nodes and bone marrow.

multiple myeloma progressive, usually fatal, malignant tumor characterized by an infiltration of bone and bone marrow and accompanied by anemia and kidney lesions.

polycythemia vera chronic, proliferative disorder of all bone marrow elements, resulting in an increased red blood cell mass.

rad unit of radiation; 450 rads in a short period of time is a lethal dose for approximately 50 percent of healthy adults exposed.

---

and the most frequent to be noted (by H. Ikui in 1948 (and 1967) in Hiroshima, and by K. Hirose and S. Fujino in 1949 (and 1950) in Nagasaki). Later studies (I. Hirose and A. Okamoto, 1961) revealed that the frequency of cataracts increased with the estimated exposure dose. The incidence, for example, for doses exceeding 100 rads was 55 percent. (Studies were done to control for the interference of senile cataracts in the data.)

Disturbances of Reproductive Function

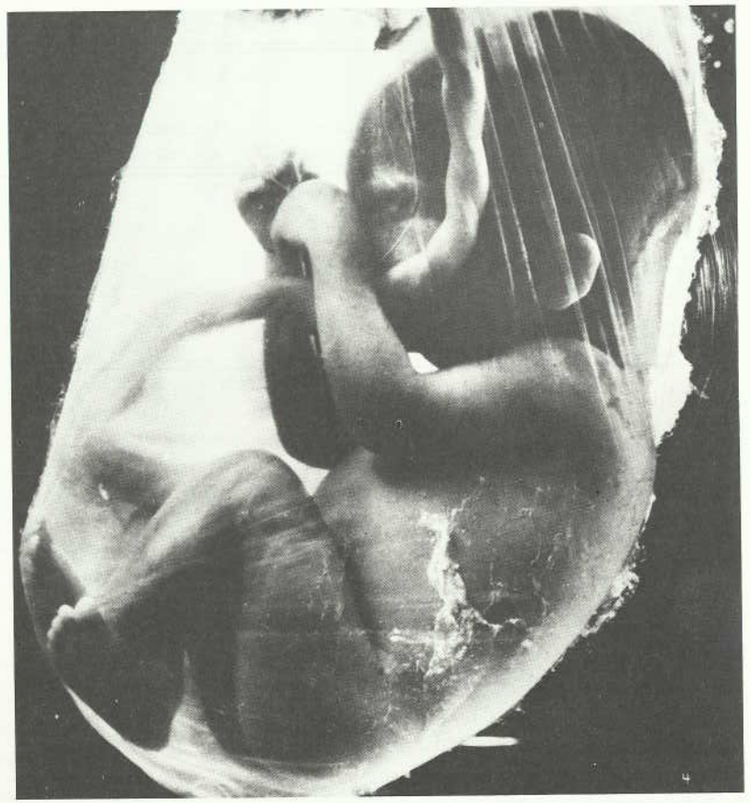
Disturbances of reproductive function are an inevitable consequence of exposure to atomic radiation. Loss of sexual desire was a frequent occurrence during the two to three months after the explosion. Investigations of the sperm of those exposed in Hiroshima were carried out by the Tokyo University Team. Of 124 cases studied in 1945, approximately one-third had markedly reduced sperm counts (less than 5×10^6/cc), indicating sterility.

According to the results of a survey performed in 1946 and 1947, there were still considerable numbers of cases of sterility among those men exposed to the bomb within 1.5 kilometers from the hypocenter. Later surveys indicated that the majority returned to almost normal in five years. According to autopsy data gathered between 1951 and 1963, testicular tissue showed greater evidence of age-related degenerative change among exposed males than among age-matched nonexposed controls.

Among women, the most prominent symptom appearing soon after the explosion was menstrual disorder. Seventy-two percent of 500 women studied showed menstrual disorders after exposure. The incidence of abnormal menstruation correlated with the distance from the hypocenter. Menstrual disturbance occurred less with thermal injury and trauma. Approximately 78 percent of those women surveyed with abnormal menstruation returned to normal by March 1946. A later survey by the Atomic Bomb Casualty Commission failed to demonstrate any evidence of reduced fertility in individuals exposed during early adulthood, the prepubertal period, or in utero.

Effects on Fetuses Exposed In Utero

Fetuses in utero were also affected by the atomic bombings. Many pregnant women died; others experienced fetal death or abortion.



Fetuses exposed in utero to acute radiation from the atomic bombings showed a marked increase in fetal and infant mortality and in mental retardation. (United Press International.)

Those babies born after a normal pregnancy were referred to as "children exposed in utero," although no accurate data exist on the exact number of those exposed in utero at the time of the bombings. Figures gathered by the Atomic Bomb Casualty Commission in 1960 revealed 2310 Hiroshima survivors who had been exposed in utero and 1562 for Nagasaki.

J. N. Yamazaki and his co-workers studied 98 women who had been pregnant on August 9, 1945, within 2 kilometers ($1\frac{1}{4}$ miles) of the hypocenter in Nagasaki. One hundred and thirteen women who had been exposed at a distance of 4 to 5 kilometers of the hypocenter were used as controls. Tables 2, 3, and 4 show the results of their survey on the incidence of fetal deaths, the mortal-

Table 2. Fetal mortality among irradiated and control groups.

Distance from Hypocenter (km)	Group	Number of Conceptions	Number of Abortions	Number of Stillbirths	Fetal Mortality (%)
0–2.0	Radiation signs	30	3	4	23.3
0–2.0	No radiation signs	68	1	2	4.4
4.0–5.0	Controls	113	2	1	2.7

Source: Yamazaki et al., 1954.

ity rate of newborns and infants, and the morbidity rate of the children up to five years after birth.

Among the 30 mothers who had been exposed within 2 kilometers of the hypocenter and who showed acute radiation symptoms, there were 7 fetal deaths, 6 neonatal and infantile deaths, and mental retardation in 4 out of the remaining cases, with an overall morbidity and mortality of 60 percent. The corresponding morbidity and mortality rates for the mothers exposed within 2 kilometers but without radiation symptoms was 10 percent and for the control mothers, 6 percent.

Microcephaly or small head size (defined as a head circumference less than two standard deviations below the age- and sex-specific mean head size) is one of the most regrettable aftereffects of atomic bomb radiation. Children with this condition were usually mentally retarded, with an extremely low intelligence quotient (IQ 16–25) and very low social adaptability. R. W. Miller and W. J. Blot (1972) studied the relation between microcephaly and radiation exposure dose. Forty-eight persons with microcephaly were found among those exposed in utero in Hiroshima, and 15 in Nagasaki. The highest incidence of microcephaly, especially when accompanied by mental retardation, was encountered in those who had been exposed before the 18th week of fetal life especially from the 3rd to the 15th weeks. In Hiroshima, a significant increase in the frequency of microcephaly was already seen among those whose mothers had received low doses of radiation, such as 10 to 19 rads.

Table 3. Neonatal and infant mortality among irradiated and control groups.

Distance from Hypocenter (km)	Group	Mothers*	Neonatal Deaths	Infant Deaths	Mortality (%)
0–2.0	Radiation signs	23	3	3	26.1
0–2.0	No radiation signs	65	3	0	4.6
4.0–5.0	Controls	110	1	3	3.6

*Mothers of living infants; stillbirths and abortions are excluded.
Source: Yamazaki et al., 1954.

Table 4. Child morbidity among irradiated and control groups.

Distance from Hypocenter (km)	Group	Mothers*	Mental Retardation in Child	Child Alive and Normal After One Year of Life	Rate of Mental Retardation (%)
0–2.0	Radiation signs	16	4	12	25
0–2.0	No radiation signs	60	1	59	1.6
4.0–5.0	Controls	106	0	106	0

*Mothers whose children were alive at time of examination.
Source: Yamazaki et al., 1954.

In general, the frequency of microcephaly increased with the increase of exposure dosage. On the other hand, in Nagasaki, no mentally retarded microcephalic children were observed under 150 rads. This difference in frequency of microcephaly with mental retardation between the two cities might be attributable to the difference in radiation quality between Hiroshima and Nagasaki, that is, to the greater proportion of neutron radiation in Hiroshima.

Growth and Developmental Disturbances

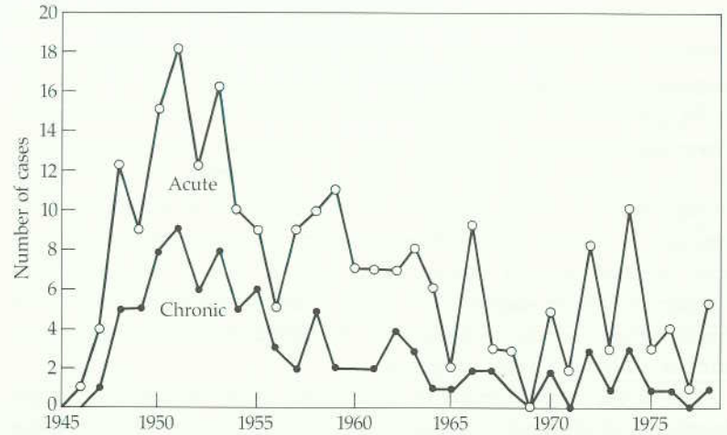
Studies performed on survivors directly exposed in childhood during the decade following the explosions suggest a detrimental effect on growth. Between 1966 and 1968, height and weight measurements were obtained by the ABCC for approximately 3200 people who were under 18 when the bomb was dropped on Hiroshima. Average heights were lower among those exposed to more than 100 rads in early childhood. The differences among the dose groups diminished with increasing age. For example, those who were under 6 at the time of the Hiroshima bomb, who were exposed to more than 100 rads, had the greatest reductions in average adult height. Children who were 6 to 11 years old with more than 100 rads exposure still had reduced adult height, but to a lesser degree. No apparent difference in mean height between the dose groups was observed for those aged 12 to 17 years at the time of the bomb. These findings were true for both Hiroshima males and females.

In Nagasaki, by contrast, a significant dose effect was not observed. Smaller heights were seen in Nagasaki females exposed to 100 or more rads when less than 5 years old at the time of the bomb, but not in Nagasaki males. The difference in effect between the two cities was again thought possibly attributable to the differing quality of radiation, however, non-radiation-related factors could not be discounted.

Malignant Tumors

The most significant radiation effect has been the induction of malignant tumors in exposed survivors. The earliest evidence of radiation-induced malignant change was the occurrence of increased leukemia in the late 1940's and early 1950's. The figure on p. 103 shows the number of leukemia cases observed annually among Hiroshima survivors exposed within 2 kilometers of the hypocenter up to 1978. The largest number was observed between 1950 and 1953 with a peak in 1951.

According to the joint studies conducted by the RERF and the Hiroshima and Nagasaki Universities Medical Schools during the period from 1950 to 1978, 202 leukemia cases were identified in a fixed group of atomic bomb survivors and their controls. The



Number of leukemia cases among Hiroshima survivors exposed within 2000 meters of the hypocenter, according to year of onset. (Courtesy of Dr. T. Ohkita, 1981.)

analysis showed that the risk for all types of leukemia, excluding chronic lymphocytic type, increased with radiation dose in both cities, except for those survivors who received less than 100 rads in Nagasaki. The risk at every dose level has been greater in Hiroshima than in Nagasaki. The incidence of chronic granulocytic leukemia increased in Hiroshima among survivors who received less than 50 rads, but in Nagasaki it was elevated significantly only among survivors who received 200 rads or more.

The leukemia-causing effect of radiation was different in relation to age at exposure. The overall incidence rate of leukemia among survivors who were exposed to more than 100 rads in Hiroshima was about 60 per 100,000 persons, about 15 times greater than that in the controls.

The occurrence of solid tumors in survivors generally increased from around 1960, after the peak of leukemia incidence. In the early stage of studies until 1968, a definite correlation between exposure distance or dose and malignancy incidence was reported for cancers of thyroid, breast, and lung.

Clinical studies in both cities in the late 1950's and early 1960's showed that the frequency of thyroid cancer was higher among survivors, especially women who were exposed to high radiation dose, than that in the nonexposed. According to the survey made

by L. N. Parker and his co-workers (1977) during the period from 1958 to 1971, the relative risk for thyroid cancer for survivors exposed to 50 rads or more was about 2.5 times that of the controls. Aside from clinically evident thyroid cancers, pathological investigations have revealed large numbers of malignant tumors of the thyroid that did not produce symptoms. Of 3067 cases autopsied up to 1968, 536 primary thyroid cancers were found, 98 percent of which were latent papillary adenocarcinomas (a specific type of thyroid cancer). The relative risk of latent thyroid cancer for those exposed to more than 50 rads was 1.4 times higher than for the nonexposed. A subsequent study of thyroid cancer after 1971 is in progress.

The death surveys made in Hiroshima about ten years after the bombing all showed that mortality from breast cancer among the exposed was higher than among the nonexposed and than the national average. M. Tokunga and his colleagues (1977) reported that during the period from 1950 to 1974, the relative risk for women exposed to 100 rads or more was about 3.3 times that of the controls. The risk was higher in heavily exposed women who were 10–39 years old at the time of the bombing, but not among those who were between the ages of 40 and 49. These differences in age susceptibility to radiation-related breast cancer suggest that hormonal factors might be involved. The dose response relationships in both cities appear to be linear and are of similar magnitude. No variation in the mean time from exposure to the appearance of breast cancer with exposure dose was noted. The histological type of breast cancer did not differ by exposure dose.

The first case of lung cancer among atomic bomb survivors in Hiroshima was reported in 1953. The radiation effect of the bombing on the lung was definite by 1958. Based on the survey up to 1974, G. W. Beebe and H. Kato (1975) reported that the relative risk for survivors exposed to 100 rads or more, compared with the nonexposed and those exposed to less than 10 rads, was 1.8 times. According to the pathological study by R. W. Cihak and coworkers (1974), small cell anaplastic carcinomas were definitely increased in heavily irradiated persons compared to the controls.

The most recent and reliable information on cancer mortality with atomic bomb radiation can be obtained from the Life Span Study, which has been in progress since 1950 by the ABCC and RERF. In addition to the thyroid, breast, and lung, people exposed to 200 rads and more demonstrated a significantly increased risk

Table 5. Bone marrow chromosome aberration in Hiroshima atomic bomb survivors.

Distance from Hypocenter (km)	Number of Cases Examined	Number of Cells Observed	With Chromosome Aberration	
			Number of Cells (%)	Number of Cases (%)
< 0.5	20	1127	262 (23.2)	18 (90.0)
0.6–1.0	21	789	101 (12.8)	11 (52.4)
1.1–1.5	18	556	1 (0.2)	1 (6.2)
1.6–2.0	23	728	0	0
2.1–3.0	23	737	3 (0.4)	1 (4.3)
Control	17	624	0	0

Source: Kamada et al., 1979.

for developing cancers of the esophagus, stomach, colon, and urinary tract. An increased risk to persons exposed to heavy radiation for the development of malignant salivary gland tumors and primary brain tumors in males has also been suggested.

Chromosome Changes

Chromosome aberration in atomic bomb survivors was initially reported by T. Ishihara and T. Kumatori in 1965. Since then, many studies have revealed that chromosomal aberrations in the peripheral blood lymphocytes (white blood cells that participate in immunity), bone marrow cells, and fibroblasts (immature fiber-producing cells of connective tissue) increased significantly in survivors who were exposed to high doses of radiation whether in utero or after birth.

The frequency of aberrant cells and of chromosomal aberrations per cell is closely associated with the increase in radiation dose, as shown in Table 5 for Hiroshima survivors.* These aberrations are all of the stable type. It is clear that the aberrations are the consequence of radiation injury and that the casualties from radiation exposure at a cellular level have not yet healed. At the present

*The frequency of aberrant cells at all dose levels is higher in Hiroshima than in Nagasaki (A. A. Awa, 1975).

time, almost all the survivors with chromosome abnormalities have normal blood values and are in good health, but the biological implication of chromosomal aberrations of somatic cells for the health of the exposed is still unknown.

Genetic Effects

Based on the experimental data, there was great concern about possible genetic effects in the offspring of survivors exposed to atomic bomb radiation in Hiroshima and Nagasaki. Careful genetic surveys have thus been carried out over the years since 1948. These studies looked at the frequency of gene mutations and chromosomal aberrations in children born to radiation-exposed parents.

In summary, genetic surveys undertaken to date have yielded no positive evidence for a genetic hazard due to atomic bomb radiation. It is possible that genetic effects do not show up so distinctly in human beings, since they have fewer pregnancies as well as fewer fetuses per pregnancy than do other mammals. Furthermore, human populations are very heterogeneous, and the chances of mutation, which would almost always be the result of having an offspring receive an identical mutant gene from each parent, would be extremely low. Thirty-seven years—only two generations—have passed since the explosion of the atomic bombs. This is a very short interval for human genetic effects. It is still too early to say definitively that there has been no genetic effect from the atomic bombs at Hiroshima and Nagasaki.

Conclusion

I believe that the pledge not to repeat the mistakes of Hiroshima and Nagasaki can be made a lasting reality if the people of the world realize and understand the suffering of those under the mushroom clouds in the two cities.

References

Hiroshima and Nagasaki: The Physical, Medical, and Social Effects of the Atomic Bombings. 1981. Edited by the Committee for the Compilation of Materials on Damage Caused by the Atomic Bombs in Hiroshima and Nagasaki. New York: Basic Books.

Kamada, N., A. Kuramoto, T. Katsuki, and Y. Hinuma. 1979. "Chromosome Aberrations in B Lymphocytes of Atomic Bomb Survivors." *Blood, 53*:1140.

Yamazaki, J. N., S. W. Wright, and P. M. Wright. 1954. "Outcome of Pregnancy in Women Exposed to the Atomic Bomb in Nagasaki." *American Journal of Diseases of Children, 87*:448.

References cited in the article that are not listed above can be found in *Hiroshima and Nagasaki: The Physical, Medical, and Social Effects of the Atomic Bombings.*