Cream wares in the Nochixtlan Valley appear in both painted and incised form in the Cholula phase at Cholula and in the Venta Salada phase in the Tehuacan Valley and probably begin earlier here than in Nochixtlan. E. Noguera, *La Cerámica de Cholula* (Editorial Guarania, Mexico City, 1954); R. MacNeish and R. Chadwick, in *The Prehistory of the Tehuacan Valley*, D. Byers, Ed. (Univ. of Texas Press, Austin, 1968), vol. 1. There are also strong parallels with the Coyotlatelco tradition of the Valley of Mexico that require further investigation. E. Rattray in *Mesoamerican Notes* **6** (1967). Historical documentation [for example, *Relación de Cholula* (1580)] also suggests strong ties between the ruling families of the Mixtec communities and the city of Cholula.
19. Brief comment on the economic importance of the Nochixtlan terrace system is provided by M. T. De la Peña, *Memorias del Instituto Nacional Indigenista*, **2** (No. 1), 39 (1950). Strikingly similar terrace structures of ancient date are reported for the Chihuahua-Sonora area of northern Mexico, and modern terraces much like those in the Nochixtlan Valley are found in the Valley of Mexico. L. C. Herold, *Univ. of Denver Dept. of Geography Technical Paper 65–1* (1967); C. S. Fletcher, *Teotihuacan to Tierra Caliente* (mimeographed paper, 1967).
20. Present findings strongly support Cook's view that much of the erosion of the Valley was an accomplished fact *before* the Spanish conquest; S. F. Cook, *Ibero-Americana* **34**, 14 (1949).
21. R. Spores, *Southwestern J. Anthropology* **20**, 15 (1964).
22. Based on figures derived from the Mexican National Census of 1960 with an increment of 10 percent for growth between 1960 and 1969.
23. Our own census of an average-sized (1041) town (Yucuita) in 1968 revealed that 284 (27 percent) townsfolk still maintaining social ties with the community and considered "family" by town residents actually lived *outside* the physical community, in such places as Oaxaca City, Puebla City, Mexico City, and in various locations in the United States. Inquiries and observations made in Yanhuitlan, Sinaxtla, Tecomatlan, Tillo, Chachoapan, and Nochixtlan would suggest that the Yucuita figures are roughly typical for both large and small towns in the Valley, but that, in some of the smaller towns (Tecomatlan and Tillo), the incidence of emigration would be even higher.
24. Derivation of reliable demographic information for Colonial and modern Mexico is a highly complex procedure, the difficulties of which cannot be discussed in the present article. Our estimates are based on consultation of numerous primary sources from the Archivo General de la Nación (Mexico City); the *Papeles de Nueva España* (Est. Tipográfico "Sucesores de Rivadeneyra," Madrid, 1905–06); *Epistolario de Nueva España* (Porrua Robredo, Mexico City, 1939–42); *Tasaciones de la Nueva España* (Archivo General de la Nación, Mexico City, 1952); *Relación de los Obispados de Tlaxcala, Michoacán, Oaxaca y otros lugares en el siglo XVI*, L. García Pimentel, Ed. (published by the author, Mexico, 1904); *Theatro Americano* (Editora Nacional, Mexico City, 1952); and from the recent demographic studies of M. T. De la Peña, W. Borah, S. F. Cook, G. Simpson, and G. Kubler. It is essential to state that the interpretations of the last mentioned writers might well be at variance with mine, and I do not pretend to speak for them. For example, I believe that Cook's estimate—based on general population trends in Mexico—of 100,000 for the Valley at the time of the Spanish conquest is far out of reason and not supported by our town-by-town assessment [S. F. Cook, *Ibero-Americana* **34**, 15 (1949)].
25. W. Borah, *Revista Mexicana de Estudios Antropológicos* **16**, 159 (1960).
26. A. Palerm and E. R. Wolf, "Ecological potential and cultural development in Mesoamerica," *Pan American Union Soc. Sci. Monograph* No. 3 (1957).
27. There is considerable documentary and archeological evidence to suggest a Mixtec expansion into the Valley of Oaxaca in Postclassic times [J. Paddock, in *Ancient Oaxaca*, J. Paddock, Ed. (Stanford Univ. Press, Stanford, Calif., 1966); I. Bernal, in *ibid.*] See R. Spores [*The Mixtec Kings and Their People* (Univ. of Oklahoma Press, Norman, 1967)] on trade, tribute, and territorial expansion in the Mixteca Alta in Postclassic and early Colonial times.
28. This research supported by Vanderbilt University Center for Latin American Studies, the Ford Foundation, and the Vanderbilt University Research Council. Geomorphological studies were conducted by M. Kirkby and A. Kirkby of Bristol University. J. Broster, C. White, E. McIntire, R. McIntire, S. Moore, and W. LaFevor, students at Vanderbilt University, and M. Winter, graduate student at the University of Arizona, have participated as members of the project field staff. K. Flannery, J. Paddock, D. Butterworth, J. Wheeler, A. W. Williams, C. E. Smith, M. E. Smith, T. Charlton, C. Moser, and F. V. Scholes have contributed direct advice and assistance. I. Bernal, J. L. Lorenzo, and L. Gamio substantially aided research through their offices with the Instituto Nacional de Antropología e Historia.

Delayed Radiation Effects in Atomic-Bomb Survivors

Major observations by the Atomic Bomb Casualty Commission are evaluated.

Robert W. Miller

The pace at which radiation effects in the Japanese survivors of the atomic bombs are being reported has recently quickened. In this article I seek to put into perspective the major findings of the Atomic Bomb Casualty Commission (ABCC).

Immediately after World War II, a joint commission of the U.S. Army and Navy made observations concerning the immediate effects of exposure to the atomic bombs in Hiroshima and Nagasaki. Upon completion of its work, the joint commission recommended that the National Academy of Sciences–National Research Council conduct a study of the long-range biomedical effects of the exposures. The Council convened an advisory group, whose study of the situation in Japan led to a Presidential directive authorizing the National Research Council (NRC) to establish an organization to evaluate the delayed effects of exposure to the bombs. Thus the Atomic Bomb Casualty Commission came into existence (*1*). Its large-scale study, begun in 1948, is a cooperative venture between the NRC, representing the United States, and the Japanese National Institute of Health. The Commission's present staff of 725 Japanese and 36 foreign nationals, including 18 U.S. professionals, is collecting and analyzing data from periodic comprehensive medical examinations, from postmortem findings, and from a review of vital certificates as they are generated.

Genetic Effects

It is commonly thought that congenital anomalies are the only measure of genetic effects among children conceived after one or both of the parents have been exposed to ionizing radiation. The studies conducted at the ABCC, however, concerned six indicators of genetic damage in the F_1 generation.

Pregnancies were ingeniously ascertained (*1*). In postwar Japan, when food was in short supply, pregnant women were allowed an extra ration of rice, beginning in the fifth month of pregnancy. When such women registered for this supplement in Hiroshima or Nagasaki, they were entered in the ABCC

The author is chief of the Epidemiology Branch at the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. This article is based on a presentation made at a symposium on the biological implications of the nuclear age, held in March 1969 to dedicate new biomedical laboratories at the Lawrence Radiation Laboratories, Livermore, California.

genetic study. From 1948 to 1953, 71,-280 pregnancies were ascertained in this way, 93 percent of all that went to term in that interval. Midwives notified ABCC of each delivery they attended, and the newborns were examined in their homes by ABCC staff physicians. About 40 percent of the children were reexamined at the clinics when they were 8 to 10 months old. The results were distributed according to five levels of radiation exposure for each parent. No influence of radiation was demonstrable in this study, which, statistical tests have shown, was likely to detect a 2-fold increase in rates of malformation or a 1.8-fold increase in rates of stillbirths and deaths of newborns. Moreover, there was no effect on birth weight or on anthropometric values at 8 to 10 months attributable to radiation exposure. The sex ratio (the proportion of males to females) for children conceived after exposure of one parent to radiation will, in theory, be diminished if the mother was irradiated, and increased if the father was (*2*). In a study of about 120,000 births, such shifts in the sex ratios were found to occur in the first 10 years following detonation of the atomic bombs but not thereafter (*3*). No effect has been found on the mortality of children conceived after exposure of their parents to the bombs in Hiroshima or Nagasaki (*4*). Thus, though laboratory experimentation leaves no doubt that irradiation is mutagenic, the effect could not be demonstrated in the F_1 generation studied by ABCC.

Cytogenetic Abnormalities

In Table 1 are summarized the results obtained in a series of studies of chromosomal abnormalities, by age group, of individuals exposed to the atomic bombs in Japan. It should be noted that, among those 30 years of age or younger at the time of the bomb who received a dose of at least 200 rad, 34 percent had complex cytogenetic abnormalities 20 years later, as compared with 1 percent of the controls (*5*). The percentage of individuals so affected who were over 30 years old at the time of the bomb was almost double the percentage for the younger group, and 4 of the 77 individuals in the older group had clones of cytogenetically abnormal cells (*6*). The frequency of complex cytogenetic abnormalities apparently increases naturally with age, from 1 percent in the younger group of the controls to 16 percent in the older group (Table 1). The complex chromosomal aberrations which occurred with increasing frequency among persons who had been over 30 years old at the time of the bomb consisted of translocations, pericentric inversions, deletions, chromatid exchanges, and centromere breaks.

Among persons who were *in utero* at the time of the bomb and whose mothers received a dose of at least 100 rad, 39 percent displayed complex chromosomal abnormalities as compared with 4 percent of the controls (*7*). Finding these abnormalities even among persons exposed during the first trimester *in utero* indicates that radiation can induce long-persisting changes in the lymphocyte precursors. In contrast to the cytogenetic defects observed following intrauterine (postconception) exposure, no such defects were found following preconception irradiation (exposure of either parent before conception of the child) (*8*).

These observations revealed that, in man, long-persisting chromosomal damage was induced even though an effect on the F_1 generation was not demonstrable.

Table 1. Frequencies, by age group, of complex cytogenetic abnormalities among Japanese survivors of the atomic bombs.

Age group at time of the bomb	Dose (rad)	Exposed: Examined (No.)	Exposed: Affected (%)	Control: Examined (No.)	Control: Affected (%)	Reference
≤ 30 years	200+	94	34	94	1	(*5*)
Over 30 years	200+	77	61	80	16	(*6*)
In utero	100+*	38	39	48	4	(*7*)
Not yet conceived	150+*	103	0			(*8*)
Not yet conceived	100+†	25	0			(*8*)

* Maternal dose. † Dose received by at least one parent.

Table 2. Effects of intrauterine exposure to the Hiroshima atomic bomb. [From Wood *et al.* (*13*)].

Gestational age (week)	Total number exposed*	Total number examined	Number with small head circumference†: Mental retardation	Number with small head circumference†: Normal intelligence
≤ 15	57‡	56‡	9	14
> 15	109	105	2§	4 ‖

* Exposure within 1800 meters of the hypocenter. † Circumference 2 or more standard deviations below average. ‡ Excludes two with preexistent Down's syndrome. § Exposed at 21 and 24 to 25 weeks, respectively. ‖ Exposed at 16, 32, 32 and 36 to 40 weeks, respectively.

Effects on the Embryo

Not long after the discovery of x-rays, case reports began to appear in the medical literature describing mentally retarded children with heads of small circumference born of mothers who had received pelvic radiotherapy during early pregnancy. Fourteen of these reports were described in a publication by Murphy in 1928 (*9*). Goldstein and Murphy (*10*) identified 16 additional cases from replies to a questionnaire sent to, and completed by, a substantial number of obstetricians. In view of these findings, it is not surprising to learn that the same abnormalities were observed among children born of women who were exposed to the atomic bomb while pregnant (*11–13*). The effect was primarily among children of women who were exposed within 15 weeks of their last menstrual period (Table 2). Of the individuals examined, 56 in this category were born of mothers who had been within 1800 meters of the hypocenter. A head circumference 2 or more standard deviations below the mean for age and sex was expected (on the basis of a normal distribution) in 1.4 persons (2.5 percent) of this group but observed in 23, of whom 9 were mentally retarded. Among the 105 individuals exposed *in utero* more than 15 weeks after the mother's last menstrual period, small head circumference was expected in 2.6 but observed in 6, of whom 2 were mentally retarded. The usual frequency of comparable mental retardation among the nonexposed of the same age in Hiroshima and Nagasaki was about 1 percent (*14*). Table 3, derived from the most recent data on the group exposed in the early weeks of pregnancy (*13*), reveals a dose-response relationship; that is, the effect diminishes in frequency and severity as the distance from the hypocenter increases.

These findings are in accord with the results of animal experimentation and with the clinical observations by Goldstein and Murphy cited above (*10*). The malformation occurred excessively only in association with high radiation dosage and not in association with the more extensive areas of heavy destruction and economic loss, which extended far beyond the high-dosage area. Estimates of the teratogenic dose range in man have not as yet been published, but about half of the mothers of affected children reported that they had signs of severe acute radiation sickness (*12*). No other anomalies occurred excessively among the survivors (*12, 13*), although many others have been observed in animals exposed experimentally to x-irradiation (*15*).

Fetal and infant mortality following exposure to the atomic bomb was not evaluated until 6 years after the event. Among women who were pregnant when exposed within 2000 meters of the Nagasaki hypocenter and who said they had had major signs of acute radiation sickness, 43 percent reported such mortality as compared with 9 percent of pregnant women in the same distance category who had not had acute radiation sickness (*16*). The excess is highly significant statistically ($P < .001$).

Growth

In 1951, as part of a comprehensive medical examination, 12 anthropometric determinations were obtained on about 2400 Hiroshima children 6 to 19 years old who had been exposed to the bomb 6 years earlier, and comparison was made with an equal number who had not been exposed (*17*). About 78 percent in each group were reexamined in 1952, and 53 percent were reexamined in 1953.

Multivariate analysis revealed that as radiation exposure increased, there were small but statistically significant decreases in body measurements at all age levels, and in growth rate at postpubertal age levels (*18*). To some extent these differences may be due to variables other than radiation exposure—for example, to economic loss due to the blast and fires.

Nagasaki adolescents who were exposed *in utero* to radiation from the atomic bomb have been studied with respect to the mean values for several anthropometric variables (*19*). The sample of heavily exposed subjects was small. Only 16 boys and 15 girls were estimated to have received doses of 50 rad or more, and only 9 of these were exposed in the first trimester of pregnancy. Some significant differences were found which were consistent with a radiation effect.

Eye Findings

In 1963 and 1964, ophthalmologic examinations were made on 1627 residents of Hiroshima and 841 residents of Nagasaki, of whom an estimated 40 percent had received doses in excess of 200 rad (*20*). In the high-dose group there were significantly more axial opacities seen by ophthalmoscope and confirmed by slit-lamp examination than in groups more distantly exposed. Most of these lesions were small, and only one was regarded as a mature radiation cataract. Another finding, more in the nature of a measure for biologic dosimetry than anything else, was a polychromatic sheen, sometimes granular, in the posterior subcapsular area of the lens as visualized by slit-lamp biomicroscopy. A dose-response relationship was demonstrated. These abnormalities did not affect visual acuity. In previous ophthalmologic examinations by ABCC, less than a dozen survivors were classified as having severe radiation cataracts, and in none was visual acuity worse than 20/70 (*21*).

In the most recent survey (*20*), there was a suggestion of a dose-related impairment of visual acuity among children who were *in utero* at the time of exposure to the bomb, but the sample size was too small for the test to be of statistical significance. In brief, though some ophthalmic effects of irradiation have been noted among atomic-bomb survivors, impairment of vision has been rare, and relatively mild.

Leukemogenesis

The leukemogenic effect of radiation in man was suspected at about the same time that teratogenic effects were—again, from case reports (*22*). Lymphoma was experimentally induced in mice in 1930 (*23*). Then, by simply reviewing the death notices published weekly in the *Journal of the American Medical Association*, Henshaw and Hawkins (*24*) found that leukemia was reported 1.7 times more often as a cause of death among U.S. physicians, a group occupationally exposed to x-rays, than among the general population of adult white males. Using the same source, Ulrich and March independently found that U.S. radiologists died significantly more often of leukemia than other physicians did (*25*). In consequence, a leukemogenic effect of exposure to atomic radiation was expected among the survivors in Hiroshima and Nagasaki, and it was found (*26*). A dose-response relationship was observed which can be attributed to no variable except radiation. A peak in occurrence was reached in 1951, more marked for the acute leukemias than for chronic granulocytic leukemia. Chronic lymphocytic leukemia, rare among the Japanese (*27*), did not increase in frequency. In children, leukemia was generally acute, as it usually is in children, the lymphocytic form being as common as the granulocytic. In all age groups acute leukemia continued to occur at higher than usual rates through 1966, whereas chronic granulocytic leukemia had fallen to near-normal rates. The ABCC study leaves no doubt that whole-body exposure to ionizing radiation at sufficiently high doses can induce leukemia in man.

Human leukemia may also be induced by partial-body irradiation, as indicated by the dose-response effect observed in British men given radiotherapy for anky-

Table 3. Radiation effect on head circumference and intelligence following intrauterine exposure to the Hiroshima atomic bomb within 15 weeks of the mother's last menstrual period. S.D., standard deviation. [From Wood *et al.* (*13*)]

Distance from hypocenter (meter)	Retarded (No.)		Normal (No.)		Total exposed*
	Head circumference > 3 S.D. below mean	Head circumference −2 to −3 S.D.	Head circumference > 3 S.D. below mean	Head circumference −2 to −3 S.D.	
≤ 1200	6	2	1	1	11
1201–1500	0†	0	2	6	23†
1501–1800	0	1	0	5	23‡
1801–2200	0	0	0	0	21‡

* Some children in the study were normal with respect to both intelligence and head circumference, thus the numbers in columns 2 to 5 do not add up to the totals in column 6. † Excludes two with preexistent Down's syndrome. ‡ One not examined.

losing spondylitis (*28*). Again, the peak was reached about 5 years after the first exposure (the first course of therapy). The predominant form in these adults was granulocytic; no increase occurred in the frequency of chronic lymphocytic leukemia. In all, 52 cases of leukemia were observed, as compared with the 5.48 expected on the basis of national mortality rates for England and Wales, and 15 persons developed aplastic anemia (perhaps subclinical leukemia) as compared with the 0.51 expected. This study, in conjunction with the ABCC study, revealed that ionizing radiation can induce more than one form of leukemia in man, but not all forms, the notable exception being chronic lymphocytic leukemia.

Irradiation is but one of several circumstances that carry exceptionally high risk of leukemia (*29*). At the highest risk yet known is the child whose identical twin develops leukemia before the age of 6 years. The probability is 1 in 5 that the second twin will develop the disease within weeks or months after the first child falls ill. In about the same category are the person with polycythemia vera treated with x-ray or phosphorus-32 (or both) and persons with Bloom's syndrome or Fanconi's anemia. The probability of developing leukemia was substantially less for heavily exposed Hiroshima survivors—about 1 in 60 individuals were so affected within 12 years of exposure. At still lower risk of leukemia are children with Down's syndrome (1 in 95 for children under 10 years old) and radiation-treated patients with ankylosing spondylitis (1 in 270 were so affected within 15 years after radiotherapy). These groups are alike in that each has a distinctive genetic feature, but these features are not of a single type. Identical twins have identical genes; Bloom's and Fanconi's syndromes are heritable disorders characterized by chromosomal fragility; in radiation-treated polycythemia vera, aneuploidy has been described in a substantial proportion of cases before radiation and chromosomal breaks are regularly found following radiotherapy; atomic-bomb survivors (and persons exposed to ionizing radiation from other sources) exhibit long-lasting chromosomal breaks; and in Down's syndrome there is congenital aneuploidy.

Leukemia in patients with polycythemia vera has been attributed to radiotherapy (*30*). It should be noted, however, that the probability of occurrence of the neoplasm was 10 times as high in these patients as it was among heavily exposed survivors of the Hiroshima bomb and 45 times as high as it was in radiation-treated ankylosing spondylitis. One must conclude either that radiation exposure or damage is greater in polycythemia vera than in the other two instances or that polycythemia vera predisposes to leukemia in the absence of radiation exposure.

Table 4. Relative risk of various childhood cancers following intrauterine or preconception exposures to diagnostic radiation.

Neoplasm	Relative risk*
Intrauterine exposure	
Stewart and Kneale (*33*)	
Leukemia	1.5
Lymphosarcoma	1.5
Cerebral tumors	1.5
Neuroblastoma	1.5
Wilms' tumor	1.6
Other cancer	1.5
MacMahon (*31*)	
Leukemia	1.5
Central-nervous system tumors	1.6
Other cancer	1.4
Graham *et al.* (*32*)	
Leukemia	1.4
Preconception exposure	
Graham *et al.* (*32*)	
Leukemia	
Mother exposed	1.6
Father exposed	1.3

* Relative risk in controls = 1.0.

Several studies, considered individually, suggest that very small exposures to radiation before conception or during pregnancy may increase by 50 percent the child's risk of leukemia. When these studies are considered collectively, however, there is reason to suspect that some fault in the methods, difficult or impossible to escape, may be implicating radiation spuriously.

The individual results are as follows. In 1958, Stewart and her associates (*31*) described a study of 677 leukemic children in England and Wales in which the proportion of mothers who reported aabdominal exposure to *diagnostic* radiation during the relevant pregnancy was twice the proportion for mothers of normal children living in the same area. A similar difference was reported with respect to 739 children with neoplasms of other kinds. It is possible that mothers of children with cancer reported their radiologic exposures more fully than the mothers of healthy children did. MacMahon (*32*) avoided this potential bias in histories obtained through interviews by studying obstetric records for irradiation during pregnancy among mothers of 304 leukemic children and 252 children with other cancer as compared with records for a 1-percent sample of all other births in the area (New England). He found a 40-percent excess of (i) leukemia and (ii) all other neoplasia among children whose mothers' records showed diagnostic radiation of the abdomen during pregnancy. Similar results were obtained by Graham *et al.* (*33*) with respect to leukemia, and by Stewart and Kneale (*34*) for each of six categories of childhood cancer. A causal relationship would be indicated if a dose-response effect could be demonstrated, if the results were consistent with those from animal experimentation, and if concomitant variables could be excluded. The exposures involved were too small to permit evaluation of a dose-response effect, there are no data from animal studies which support the observations in man, and the condition being treated by the radiologic procedure, rather than the x-ray exposure itself, could, in theory at least, be the oncogenic factor.

Recently Graham and his associates (*33*) described an excess of leukemia among children whose mothers *or* fathers gave histories of diagnostic radiation exposure up to a decade before the children were conceived. Again, there are no animal studies to support this observation. Moreover, in a prospective study (*35*) of 22,400 children conceived after their parents had been heavily exposed to radiation from the atomic bombs in Hiroshima or Nagasaki, no excess of leukemia was found.

Table 4 summarizes the results following very small doses of x-ray, and indicates that such irradiation was equally oncogenic whether exposure occurred before conception or during pregnancy, whether the neoplasm studied was leukemia or any other major cancer of childhood, and whether the study was based on interviews, which may be biased, or on hospital records. Taken in the aggregate, the similarity of results in the absence of a dose-response effect or of supporting data from animal experimentation raises a question about the biologic plausibility of a causal relationship. In particular one must ask, in the absence of demonstrable mutagenic or cytogenetic abnormalities in the F_1 generation, if irradiation of the parent prior to conception is likely to induce leukemia in the child.

Other Cancer

Wanebo *et al.* (*36*) have recently reported that "accumulated information . . . strongly suggests that exposure to ionizing radiation has increased the risk of lung cancer among atomic bomb survivors." These investigators observed 17 such cases, as compared with 9 expected (dose, 90 rad or more). A weakness in the report was the finding that the lung cancers induced were nonspecific as to histologic type, rather than of the undifferentiated or small-cell type, as in U.S. uranium miners and in workers heavily exposed to mustard gas, a radiomimetic chemical (*37*).

Wanebo *et al.* (*38*) have reported that "information on breast cancer among survivors of the atomic bombings of Hiroshima and Nagasaki has now accumulated to the point where a fairly definite carcinogenic effect seems established." Six cases were observed among women who were exposed to 90 rad or more, as compared with 1.53 cases expected—an excess of only 4.5 cases. There was no specificity as to histologic type.

It may be difficult or impossible to avoid certain biases that could produce such a small excess—for example, unequal detection of cases with respect to exposure category, or dissimilar cancer risks in relation to some variable other than radiation which distinguished the heavily exposed from others in the study. Wanebo *et al.* considered the possibility of biases and believed that none were present. The absence of a dose-response relationship makes interpretation of the results difficult, as does the small or uncertain effect observed in studies of other exposed persons.

Wood *et al.* (*39*) have recently described an excess of thyroid cancer among Japanese survivors of the atomic bomb. The increase was greater in women than in men, the effect being proportionate to the radiation dose, but no specificity as to cell type was found. These observations are in accord with the results of animal experimentation and with the increase in frequency of thyroid cancer following therapeutic radiation early in childhood (*40*).

One may conclude that, among the Japanese survivors of the atomic bomb, only leukemia and thyroid cancer have been shown to be radiation-induced. The evidence pertaining to cancer of the breast or lung is still very much in doubt.

Mortality

Animal experimentation has shown that ionizing radiation can induce a shortening of life span which is attributable to no specific disease but to an accelerated occurrence of disease in general (*41*). The ABCC has conducted a study of life span among the survivors of the atomic bombs. The most recent published analysis concerns deaths in Hiroshima and Nagasaki, in the decade 1950 to 1960, in a sample of 99,393 persons—survivors of all ages—and a similar group of individuals not exposed to the bomb (*42*). When leukemia was excluded as a cause of death, the mortality ratios for exposed persons who had been within 1200 meters of the hypocenter in Hiroshima and Nagasaki were elevated by about 15 percent, an increase that was statistically significant when the data for both sexes and both cities were evaluated through a combined test. The increase was greater for women than for men and faded with time, reaching near-normal rates in about 1955. In another analysis of mortality, now in progress, the data through 1966 are being evaluated to determine if, after an extended period of latency, mortality may again be increased.

Summary

Since 1948 the ABCC has been evaluating the health of survivors of the atomic bombs in Hiroshima and Nagasaki. In a study of about 70,000 children conceived after the explosion, six indicators of genetic damage failed to reveal an unequivocal effect of radiation. Furthermore, this group displayed no evidence of cytogenetic abnormality, in contrast to the increased frequency of complex chromosomal aberrations found among those exposed *in utero* or at any time during the entire life span. The effect was most pronounced among persons whose exposures occurred when they were 30 years of age or older.

Although a wide variety of congenital malformations have been produced in experimental animals by irradiation of the pregnant mother, the only anomaly observed among the Japanese survivors to date has been small head circumference associated with mental retardation, the effect being proportionate to the radiation dose.

The ABCC study leaves no doubt that whole-body irradiation in sufficient dose is leukemogenic in man. A similar effect following partial-body irradiation has been observed among British men given radiotherapy for ankylosing spondylitis. In both studies the effect was proportionate to the dose, the peak occurred about 6 years after first exposures, and the increase was in acute leukemias and chronic granulocytic leukemia, not in the chronic lymphocytic form of the disease.

In the past few years, a high risk of leukemia has been associated with several human attributes and with radiation exposure. These circumstances have in common an unusual genetic feature, though not of a single type.

In several studies conducted in the United States or Great Britain, very small doses of x-ray were reported to be equally oncogenic whether exposure occurred before conception or during intrauterine life; whether the neoplasm studied was leukemia or any other major cancer of childhood; and whether the study was based on interviews, which are subjective, or on hospital records, which are not. Among the features that argue against a causal relationship are the similarity of results despite the dissimilarity of subject matter and, with regard to radiation before the child's conception, the failure, in a prospective study by ABCC, to find an excess of leukemia in 22,400 children conceived after their parents had been heavily exposed to radiation from the atomic bomb.

Increases in cancers other than leukemia have recently been reported among the Japanese survivors. Twice the normal frequency of lung cancer was found among persons exposed to doses of 90 rad or more, in a study handicapped by failure to demonstrate specificity with regard to histologic type, as in U.S. uranium miners. A report of an excess of breast cancer was based on 6 cases observed as compared with 1.53 expected among women who were exposed to doses of 90 rad or more. Certain biases, difficult or impossible to avoid, could produce this small excess. Thyroid cancer, on the other hand, does appear to have been induced by radiation, since a dose-response relationship was apparent and the results are consistent with those observed following therapeutic irradiation.

Other effects attributable to radiation but relatively small in magnitude were an increase in general mortality, exclusive of death from leukemia, during the first 10 years after exposure; a statistically significant but biologically small retardation in growth and development; infrequent radiation cataracts, none of which greatly diminished visual acuity; and a polychromatic sheen on the posterior subcapsule of the lens of the eye, which caused no disability but was related to radiation dose.

References and Notes

1. J. V. Neel and W. J. Schull, "The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki," *Nat. Acad. Sci. Nat. Res. Counc. Publ. No. 461* (1956).
2. J. V. Neel, *Changing Perspectives on the Genetic Effects of Radiation* (Thomas, Springfield, Ill., 1963).

3. W. J. Schull, J. V. Neel, A. Hashizume, *Amer. J. Hum. Genet.* **18**, 328 (1966).
4. H. Kato, W. J. Schull, J. V. Neel, *ibid.*, p. 339.
5. A. D. Bloom, S. Neriishi, N. Kamada, T. Iseki, R. J. Keehn, *Lancet* **1966-II**, 672 (1966).
6. A. D. Bloom, S. Neriishi, A. A. Awa, T. Honda, P. G. Archer, *ibid.* **1967-II**, 802 (1967).
7. A. D. Bloom, S. Neriishi, P. G. Archer, *ibid.* **1968-II**, 10 (1968).
8. A. A. Awa, A. D. Bloom, M. C. Yoshida, S. Neriishi, P. G. Archer, *Nature* **218**, 367 (1968).
9. D. P. Murphy, *Surg. Gynecol. Obstet. Int. Abstr. Surg.* **47**, 201 (1928).
10. L. Goldstein and D. P. Murphy, *Amer. J. Roentgenol. Radium Ther. Nucl. Med.* **22**, 322 (1929).
11. G. Plummer, *Pediatrics* **10**, 687 (1952).
12. R. W. Miller, *ibid.* **18**, 1 (1956).
13. J. W. Wood, K. G. Johnson, Y. Omori, *ibid.* **39**, 385 (1967).
14. J. W. Wood, K. G. Johnson, Y. Omori, S. Kawamoto, R. J. Keehn, *Amer. J. Public Health Nat. Health* **57**, 1381 (1967).
15. R. Rugh, *Ann. Rev. Nucl. Sci.* **9**, 493 (1959).
16. J. N. Yamazaki, S. W. Wright, P. M. Wright, *Amer. J. Dis. Child.* **87**, 448 (1954).
17. E. L. Reynolds, *Atomic Bomb Casualty Comm. Tech. Rep.* (1954), pp. 20–59.
18. J. V. Nehemias, *Health Phys.* **8**, 165 (1962).
19. G. N. Burrow, H. B. Hamilton, Z. Hrubec, *J. Amer. Med. Ass.* **192**, 97 (1965).
20. M. D. Nefzger, R. J. Miller, T. Fujino, *Amer. J. Epidemiol.* **89**, 129 (1968).
21. D. G. Cogan, S. F. Martin, H. Ikui, *Trans. Amer. Ophthalmol. Soc.* **48**, 62 (1950); R. J. Miller, T. Fujino, M. D. Nefzger, *Arch. Ophthalmol.* **78**, 697 (1967).
22. C. E. Dunlap, *Arch. Pathol.* **34**, 562 (1942).
23. C. Krebs, H. C. Rask-Nielsen, A. Wagner, *Acta Radiol. Suppl.* **10**, 1 (1930).
24. P. S. Henshaw and J. W. Hawkins, *J. Nat. Cancer Inst.* **4**, 339 (1944).
25. R. C. March, *Radiology* **43**, 276 (1944); H. Ulrich, *N. Engl. J. Med.* **234**, 45 (1946).
26. J. H. Folley, W. Borges, T. Yamawaki, *Amer. J. Med.* **13**, 311 (1952); A. B. Brill, M. Tomonaga, R. M. Heyssel, *Ann. Intern. Med.* **56**, 590 (1962); O. J. Bizzozero, Jr., K. G. Johnson, A. Ciocco, *N. Engl. J. Med.* **274**, 1095 (1966).
27. S. C. Finch, T. Hoshino, T. Itoga, M. Ichimaru, R. H. Ingram, Jr., *Blood* **33**, 79 (1969).
28. W. M. Court Brown and R. Doll, *Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis* (Her Majesty's Stationery Office, London, 1957); *Brit. Med. J.* **1965-II**, 1327 (1965).
29. R. W. Miller, *Cancer Res.* **27**, 2420 (1967).
30. B. Modan and A. M. Lilienfeld, *Medicine* **44**, 305 (1965).
31. A. Stewart, J. Webb, D. Hewitt, *Brit. Med. J.* **1958-I**, 1495 (1958).
32. B. MacMahon, *J. Nat. Cancer Inst.* **28**, 1173 (1962).
33. S. Graham, M. L. Levin, A. M. Lilienfeld, L. M. Schuman, R. Gibson, J. E. Dowd, L. Hempelmann, *Nat. Cancer Inst. Monogr.* **19**, 347 (1966). Subsequent reanalysis of the data for children under 4 years old suggested that cofactors are involved—for example, maternal history of fetal mortality, or virus infection in the child more than 12 months before the diagnosis of leukemia [R. W. Gibson, I. D. J. Bross, S. Graham, A. M. Lilienfeld, L. M. Schuman, M. L. Levin, J. E. Dowd, *N. Engl. J. Med.* **279**, 906 (1968)].
34. A. Stewart and G. W. Kneale, *Lancet* **1968-I**, 104 (1968).
35. T. Hoshino, H. Kato, S. C. Finch, Z. Hrubec, *Blood* **30**, 719 (1967).
36. C. K. Wanebo, K. G. Johnson, K. Sato, T. W. Thorslund, *Amer. Rev. Resp. Dis.* **98**, 778 (1968).
37. J. K. Wagoner, V. E. Archer, F. E. Lundin, Jr., D. A. Holaday, J. W. Lloyd, *N. Engl. J. Med.* **273**, 181 (1965); S. Wada, Y. Nishimoto, M. Miyanishi, S. Kambe, R. W. Miller, *Lancet* **1968-I**, 1161 (1968).
38. C. K. Wanebo, K. G. Johnson, K. Sato, T. W. Thorslund, *N. Engl. J. Med.* **279**, 667 (1968).
39. J. W. Wood, H. Tamagaki, S. Neriishi, T. Sato, W. F. Sheldon, P. G. Archer, H. B. Hamilton, K. G. Johnson, *Amer. J. Epidemiol.* **89**, 4 (1969).
40. S. Lindsey and I. L. Cheikoff, *Cancer Res.* **24**, 1099 (1964); L. H. Hempelmann, *Science* **160**, 159 (1968).

→ J. B. Storer, *Radiation Res.* **25**, 435 (1965).

→ S. Jablon, M. Ishida, M. Yamasaki, *ibid.*, p. 25.

The Computer and Individualized Instruction

An automated information system now supports the development of individually prescribed instruction.

William W. Cooley and Robert Glaser

One of the most important potential uses of computers in schools is their use to individualize the educational process. However, as the history of attempts at individualization indicates, little can be accomplished unless the educational process is operationally defined and translated into specific school practices. The basic requirement for this is the presentation of an instructional model which underlies and generates (i) the instructional procedures, materials, and school environment and (ii) the data and research information needed for performing the desired educational functions effectively.

The authors are co-directors of the Learning Research and Development Center, University of Pittsburgh, Pennsylvania.

Therefore, before any fruitful discussion on how the computer might facilitate such education can begin, it is necessary to specify just how individualization is to be accomplished. The instructional model can serve as the beginning of a system which can then be improved on the basis of information obtained from the model's application. If there is no model, or if it is ambiguous, it is difficult to structure operations and essentially impossible to make continuous improvements in the total educational system. It is in this light, and with this as a base for discussing the individualized school and the computer, that we present a model of educational practice which can underlie individualized instruction.

Individualized education is essentially the adaptation of instructional practices to individual requirements. Three major factors are involved, each of which defines a set of variables in the system: (i) educational goals, (ii) individual capabilities, and (iii) instructional means. *Goals* are defined to suit the individual, as when individuals choose different courses of instruction for different desired vocations. The term *individual capabilities* refers to the capabilities that the individual brings to a particular instructional situation; these are influenced by prior background and schooling. *Instructional means*, which include what is taught and how it is taught, are dictated by both the nature of the individual's capabilities and the nature of his educational goals. These three factors may change in the course of one's education or one's life, but in any particular span of time, during a specific teaching act, it is assumed that a particular educational goal or level of competence is to be attained; that the individual has particular capabilities; and that there is available a set of instructional means and conditions relevant to assessed capabilities and to criteria of competence.

Thinking about the educational process in this way suggests the following general instructional model, which is presented as a sequence of operations (*1*).

1) The goals of learning are specified in terms of observable student be-