A Review of Forty-Five Years Study of Hiroshima and Nagasaki Atomic Bomb Survivors

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Aging

The hypothesis that exposure to ionizing radiation accelerates the aging process has been actively investigated at ABCC-RERF since 1958, when longitudinal cohort studies of the Adult Health Study (AHS) and the Life Span Study (LSS) were initiated. In their 1975 overall review of aging studies related to the atomic bomb (A-bomb) survivors, Finch and Beebe concluded that while most studies had shown no correlation between aging and radiation exposure, they had not involved the large numbers of subjects required to provide strong evidence for or against the hypothesis. Extending LSS mortality data up to 1978 did not alter the earlier conclusion that any observed life-shortening was associated primarily with cancer induction rather than with any nonspecific cause.

The results of aging studies conducted during the intervening 15 years using data from the same populations are reviewed in the present paper. Using clinical, epidemiological, and laboratory techniques, a broad spectrum of aging parameters have been studied, such as postmortem morphological changes, tests of functional capacity, physical tests and measurements, laboratory tests, tissue changes, and morbidity.

With respect to the aging process, the overall results have not been consistent and are generally thought to show no relation to radiation exposure. Although some preliminary results suggest a possible radiation-induced increase in atherosclerotic diseases and acceleration of aging in the T cell-related immune system, further study is necessary to confirm these findings.

In the future, applying the latest gerontological study techniques to data collected from subjects exposed 45 years ago to A-bomb radiation at relatively young ages will present a new body of data relevant to the study of late radiation effects.

INTRODUCTION

The hypothesis that ionizing radiation exposure accelerates aging has been actively investigated at ABCC-RERF since 1958, when longitudinal cohort studies of the Adult Health Study (AHS) and Life Span Study (LSS) were initiated. This hypothesis arose out of experimental work on rats and mice in the late 1930s and 1940s in which irradiated animals had a shorter life span and appeared to age more rapidly than the nonirradiated controls. These observations, which have been confirmed repeatedly, led to the hypothesis that radiation-induced life-shortening is mechanistically equivalent to natural senescence. The idea of equivalence was first based on actuarial observations of an increase in the mortality rate from all causes of death, with an apparent shift of diseases characteristic of older age to younger age groups. Other phenomena that appear to support this hypothesis of equivalence include radiation-induced alteration of the physical appearance of animals such that they assume
the character of aged animals including graying of the fur, reduced activity level, occurrence of
cataract, loss of reproductive capacity, etc.\textsuperscript{6–8}.

However, Mole criticized the idea of equivalence of radiation-induced life-shortening and
natural aging, and commented on the absence of conclusive data on the cause of death in earlier
experimental work\textsuperscript{9}). Upton also noted in his reviews that the nonneoplasmic changes known
to follow irradiation seemed insufficient to account for the life-shortening effect being observed,
and that some of them bore little resemblance to natural senile changes\textsuperscript{10–12}). Experimental work
by Lindop et al. using the age-specific mortality rate and with greater attentiveness to the cause
of death indicated that the process was not identical to natural aging\textsuperscript{13,14}).

In many of the papers reviewed, there is considerable discussion about the specifically or
nonspecificity of the life-shortening observed in a variety of experimental situations\textsuperscript{15}). The word
“specific” implies that the irradiated animals who die earlier than their controls exhibit a
characteristic spectrum of diseases or causes of death that differ from the spectrum seen in the
nonirradiated controls. If “nonspecific” life-shortening induced by radiation exposure, on the
other hand, is compatible with advanced or accelerated aging, radiation should not modify the
spectrum of normally occurring diseases. However, this notion may not be substantiated by
experimental evidence. Thus, the idea of a nonspecific effect of irradiation superimposable on
physiological aging becomes conceptually improbable. Recently, the discussion has been
centered on whether radiation exposure may produce life-shortening by induction of tumors and
how much of the observed shortening can be accounted for by neoplastic diseases. Though never
defined clearly, the words “specific” and “nonspecific” have therefore been taken to indicate
neoplastic and nonneoplastic contributions to life-shortening\textsuperscript{15,16}). In his systematic review of
the literature and reanalysis of some of the older data, Walburg concluded that radiation exposure
at moderate-to-low doses (under 300 rad [3.0 Gy] of low-LET (Linear Energy Transfer) radiation)
shortens life, explained principally by the induction or acceleration of neoplastic diseases\textsuperscript{6}). This

conclusion was supported by Storer and Sanders\textsuperscript{17}).

Numerous attempts have been made to establish a theory of aging to specify its essential
mechanisms, such as the immunological theory, the neuroendocrine theory, the free radical theory,
the cross-linkage theory, the somatic mutation theory, the error theory, and the program
theory\textsuperscript{18–22}). However, to date, there seems to be no satisfactory theory that explains the variety
of changes associated with the aging process\textsuperscript{18–22}), thus providing no clear-cut direction for
research on radiation-induced aging. Experimental work on aging is also hampered somewhat
by the lack of any direct measure of senescence other than in terms of life span, and the difficulty
in deciding whether pathological processes in old animals are the cause of aging or the effects
of aging\textsuperscript{15}).

Some attempts have been made to relate the possible effect of radiation-induced life-shortening
to nonspecific, diffuse, subclinical deterioration of tissues that might promote the onset of old-age
diseases to roughly the same degree as natural senescence. A great variety of degenerative changes
occur in irradiated tissue\textsuperscript{11,23}), and some of these superficially resemble senescent changes, even
though there are profound differences between them\textsuperscript{6}).

Casarett proposed that radiological aging be ascribed to the damage of endothelial cells of
the fine vasculature, leading to fibrotic changes of the arterioles and of the interstitial collagenous
Although Casarett's proposal was well founded, as it is known that radiation may cause interstitial fibrillar density and capillary fibrosis, this approach requires further substantiation.

Similarly, one might assume that alterations of the immune system are related to radiation-induced aging. However, relevant data are thought to be inconclusive.

Recently, other hypotheses related to molecular changes have been considered. Cutler reviewed the concept of the primary aging process, in which cross-linkages between biologically important molecules effected by various agents are postulated to be the origin of natural senescence and of possible radiation-induced changes. This hypothesis has received little experimental support when applied to cellular and extracellular constituents, such as collagen and age pigments. Hart discussed a more recent complementary working hypothesis that envisages the aging process as a sequence of events involving the induction of DNA damage and its subsequent manifestation at the physiological level. The ability of the system to repair DNA damage and the redundancy of the genetic information for vital functions within the system are the factors controlling the manifestation of such damage. These hypotheses have not yet been formalized and require further substantiation.

Most data on occupationally exposed groups and groups exposed to therapeutic uses of ionizing radiation have suggested that radiation-induced life-shortening in humans is not due primarily to nonspecific causes, but is due to the induction of neoplasms.

In 1956, Warren reported that radiologists had a shorter mean life span than doctors not routinely exposed to radiation, and they seemed to die at younger ages from practically every cause of death. Warren's method of comparison was criticized by Seltser and Sartwell, who found that radiologists would in fact be expected to die at younger ages, because there were proportionately fewer elderly radiologists. However, in their own cohort study on medical specialists, Seltser and Sartwell found that compared to other medical specialists, radiologists suffered higher mortality rates not only from cancer but also from cardiovascular-renal diseases and other nonneoplastic diseases.

In the United Kingdom, Court-Brown and Doll reported that they could not find excess mortality among radiologists apart from that attributed to cancer. A 20-year extension of the British radiologist study provided no support for a nonspecific life-shortening after radiation exposure. Smith and Doll reported on about 14,000 patients with ankylosing spondylitis who had been given a single course of X rays between 1935 and 1954. An excess of deaths from leukemia and cancers of the heavily irradiated sites was observed among the patients with ankylosing spondylitis, but the data did not support a nonspecific life-shortening effect. Aware of the peculiarity of their findings, Seltser and Sartwell extended their study, which revealed results similar to their earlier findings: U.S. radiologists seem to be the only human population apparently exhibiting radiation-induced nonspecific life-shortening.

An extensive review through 1975 was conducted by Finch and Beebe, based on numerous studies of aging among the A-bomb survivors. Cause-specific mortality in the LSS was examined for 82,000 survivors and 27,000 individuals who were not in either city at the time of the bombings. The relative risk was adjusted for age, sex, and city for subjects exposed to ≥ 100 rad [1 Gy] and those exposed to < 10 rad [0.1 Gy]. These subjects clearly revealed the well-
established carcinogenic effect of radiation exposure, but provided no convincing evidence that other causes of death, both in general and specific individual causes of death, were influenced in any way by radiation exposure. The age-specific mortality rates were calculated for low-dose vs. high-dose groups, for all natural causes of death except malignant neoplasms, and for time intervals from 1950 to 1972. These rates also suggested no generalized increase in mortality from natural causes that the hypothesis of accelerated aging would seem to require. Examinations of a wide variety of aging parameters in subjects who participate in RERF's biennial AHS examinations have also yielded mostly negative results. Only two of many age-related indices appear to be related to radiation. Yano and Ueda found an increase in certain electrocardiographic changes in heavily exposed males, but this was confined to a single 10-year age group, i.e., those ranging in age from 50 to 59. A second study, in which two histological changes in the testis were related to age, revealed that tubular sclerosis is also related to radiation exposure. Other potential parameters of aging have been shown to be quite reliably related to radiation exposure, especially lenticular opacity and neoplasms, but these relationships seem better understood as specific effects of radiation rather than as evidence of radiation-accelerated, nonspecific aging.

Earlier cytogenetic studies suggested a possible relationship between age and chromosome number. Yet, based on studies still in progress, these findings are now in doubt. However, Finch and Beebe suggested further investigations on aging, because the hypothesis had never been fully tested in humans and because the experience of the A-bomb survivors could be expected to provide definitive human data on the subject.

In this article, we will examine the status of aging studies conducted at ABCC-RERF by reviewing the results accumulated during the last 15 years.

Mortality Studies of A-bomb Survivors

An extended analysis of LSS mortality data up to 1974 was performed by Beebe et al. Deaths from nonneoplasmic diseases totaled about 14,000 out of 82,000 survivors. In the irradiated subjects, cerebrovascular diseases, other circulatory diseases, and diseases of the digestive system showed no evidence of an increase. Deaths due to diseases of the blood and blood-forming organs increased, but diagnoses that possibly attributed these deaths to cancer cast some doubt on this assumption. In their most recent report using data until 1978, Kato et al. calculated age-specific death rates for all nonneoplastic causes (taken at 4-year intervals and adjusted for city and sex within each time period) separately for the groups exposed to 0–0.09 Gy and to ≥1 Gy. The results did not change from earlier reports. The survival curve excluding deaths from malignant neoplasms for this cohort did not differ by dose over the whole period of 1950 through 78. These findings, as repeatedly pointed out, do not corroborate the hypothesis that radiation may accelerate natural aging. Investigations to test this hypothesis using LSS mortality data are ongoing, and some of the results will be described in this report.

Postmortem Studies of Aging

Pathology studies conducted by ABCC-RERF investigators during the past 15 years are summarized in Table 1. Although a number of age-related pathological changes have been reported,
none of them has shown any association with ionizing radiation. Focal cardiac myocytolysis, a unique, histologically recognizable cardiac lesion which might reveal the presence of an ischemic episode, was more common in older persons, but there was no evidence that radiation exposure increased the occurrence of this lesion. During a series of clinical-pathological studies of the heart, findings related to papillary muscle fibrosis and small vessel sclerosis turned out to be almost identical to findings for focal cardiac myocytolysis. A morphological study of central nervous system aging was performed, in which small vessel arteriosclerosis, senile plaques, neurofibrillary tangles, granulovascular degeneration, and hypoglossal nucleus hyaline cytoplasmic inclusions were quantified. The presence of neurofibrillary tangles, particularly in the hippocampus, was the best indicator of chronological age, but this appeared to be independent of radiation exposure. A pathological study of the central nervous system is now under way, although its scale has been reduced in accordance with a marked reduction in autopsy cases in recent years.

### Table 1. Age-related pathological changes examined in RERF studies

| Study                                | Ref. | Chronological Age Correlation | Radiation Effect |
|--------------------------------------|------|-------------------------------|-----------------|
| Pancreatic Ductal Epithelial Change  | 56   | ↑ With age                    | None            |
| Neurofibrillary Tangle               | 57   | ↑ With age                    | None            |
| Senile Plaque                       | 57   | ↑ With age                    | None            |
| Granulovascular Degeneration        | 57   | ↑ With age                    | None            |
| Focal Cardiac Myocytolysis          | 58   | ↑ With age                    | None            |
| Papillary Muscle Fibrosis (focal)    | 59   | ↑ With age                    | None            |
| Urinary Bladder Transitional Epithelium | 61   | No relation                  | None            |

NOTE: "↑" = increases.

Functional or Physical Tests

To measure age-related changes, AHS participants underwent numerous functional and physical tests which vary greatly in their relationship to chronological age. These tests are listed in Table 2. Both systolic and diastolic blood pressure increase with age, although the latter tends to decrease in those older than 70. The forced vital capacity, a useful clinical test of respiratory performance, indicated a progressive decline in capacity with age. However, for the above-mentioned items there is no indication that change with age depends in any way on radiation exposure. Mihara et al. conducted a study to examine serial changes on chest radiography.
Hollingworth first attempted to devise an index of physiological age based on measurements of a number of physiological variables. Belsky et al. performed a similar study to look for evidence of radiation-induced aging. In their study, scores on six tests — grip strength, audiometry, vibratory perception, amplitude of visual accommodation, skin elasticity, and visual reaction time — were combined in a multiple-regression equation to provide a “physiological age” score for each individual. No association was found between physiological age and radiation. Yet each of the six parameters used to calculate physiological age individually showed a close relationship to age. Several highly statistically significant differences were seen in tests of grip strength between the control group (0–9 rad [0–0.09 Gy]) and the population exposed to ≥100 rad [1 Gy], and in the audiometric tests between the control group and the 50- to 99-rad [0.5–0.99 Gy] exposure group. Except for sporadic instances, there did not appear to be any consistent pattern of differences to suggest aging effects due to radiation exposure.

A follow-up study of physiological age is under way. With respect to survival 15 years after Belsky's study, one group which had been classified as physiologically old was compared with a second group equivalent in chronological age but considered to be physiologically young. A higher mortality rate that was not associated with either radiation exposure of cancer was observed among the physiologically old group.

Although the pattern of age-related changes varies among organs and measurements, deterioration of function with advancing age seems to be universal in all organs. Because environmental factors including nutrition, smoking, drug use, etc. may partly influence these

### Table 2. Functional or physical tests performed on Adult Health Study participants

| Test or Measurement                   | Ref. | Chronological Age Correlation | Radiation Effect |
|--------------------------------------|------|-------------------------------|------------------|
| Forced Vital Capacity                | 62, 63 | ↓ With age*                  | None             |
| Grip Strength                        | 63   | ↓ With age                    | In >100 rad (1 Gy) group |
| Visual Acuity                        | 63   | ↓ With age                    | Not consistent   |
| Vibrometer                           | 63   | ↓ With age                    | Not consistent   |
| Audiometry                           | 63   | ↓ With age                    | In 50–99 rad (0.5–0.99 Gy) group |
| Amplitude of Visual Accommodation    | 63   | ↓ With age                    | Not consistent   |
| Light Extinction                     | 63   | ↓ With age                    | Not consistent   |
| Skin Elasticity                      | 63   | ↓ With age                    | Not consistent   |
| Physiologic Age                      | 63   | ↑ With chronologic age        | None             |
| Cardiac Performance                  | 64   | Not consistent                | None             |
| Systolic Blood Pressure              | 65, 66, 67 | ↑ With age                  | None             |
| Diastolic Blood Pressure             | 65, 66, 67 | ↑ With age until 60–69 yrs  | None             |
| Aortic Arch Diameter                 | 68   | ↑ With age*                   | None             |
| Cardio-thoracic Ratio                | 68   | ↑ With age*                   | None             |
| Transverse Thoracic Diameter         | 58   | ↑ With age                    | None             |

NOTE: "↑" and "↓" = increases and decreases, respectively.

* Results from a longitudinal study.
Table 3. Laboratory tests used in studies of aging and radiation exposure

| Test                                      | Ref.   | Chronological Age Correlation | Radiation Effect                                      |
|-------------------------------------------|--------|-------------------------------|-------------------------------------------------------|
| Urine Protein                             | 66     | ↑ With age                    | None                                                  |
| Blood Sedimentation Rate                  | 66, 71 | ↑ With age                    | Positive                                              |
| Glucose Tolerance Test                    | 70     | ↑ With age in borderline type | Positive only in younger survivors                    |
| α, β-globulin                             | 72     | ↑ With age                    | Positive                                              |
| Lymphocyte Cytotoxicity                   | 73     | ↑ With age                    | None                                                  |
| Whole-blood Phagocytic Activity          | 74     | No relation                   | None                                                  |
| Serum Anti-EB Titors                      | 75, 82 | ↑ With age                    | Equivocal                                             |
| Lymphocyte Count                          | 76     | ↓ After age 70                | None                                                  |
| PHA Response                              | 77     | ↓ With age                    | Positive                                              |
| Con A-induced Suppressor T Lymphocytes    | 78, 83 | ↓ With age                    | Equivocal                                             |
| Helper/Inducer T Cells                    | 79, 83 | ↓ With age, especially at >75 yr | None                                                  |
| B Cells and Monocytes                     | 79, 83 | ↑ With age, especially at >75 yr | None                                                  |
| MLC Response                              | 80     | ↓ With age (suggestive)       | Especially at >15 yr ATB                              |
| Natural Killer Cell Activity              | 81     | ↑ With age                    | None                                                  |
| Circulating Immune Complex                | 81     | ↑ With age                    | None                                                  |
| Number of T Cells                         | 83     | ↓ With age                    | Positive at >30 yr ATB                                |
| Somatic Mutation                          |        |                               |            |
| T-Lymphocyte HPRT                         | 84, 87 | ↑ With age                    | Weak positive                                         |
| Erythrocyte GPA                           | 85, 87 | ↑ With age                    | None                                                  |
| T-Lymphocyte TCR                          | 86, 87 | ↑ With age                    | Positive                                              |
| T-Lymphocyte HLA-A                        | 87     | ↑ With age                    | Study in progress                                     |
| Mitotic Index                             | 88     | ↓ With age                    | None                                                  |
| Chromosome Aneuploidy                     | 89, 90 | ↑ With age                    | None                                                  |

NOTE: ATB = at the time of the bombings; MLC = mixed lymphocyte culture; PHA = phytohemagglutinin; GPA = glycoprotein-A; HPRT = hypoxanthine guanine phosphoribosyl transferase; and TCR = T-cell receptor. "↑" and "↓" = increases and decreases, respectively.
age-related changes, continued study taking these factors into account will be required.

**Laboratory Tests**

Table 3 briefly summarizes the laboratory data derived from studies of aging and radiation. Although the relationship with age for many parameters is apparent, the association between these parameters and radiation dose has been inconsistent. For example, the prevalence of impaired glucose tolerance increased with age, but radiation effects were suggested only for younger survivors. On the other hand, blood sedimentation rate and serum α- and β-globulin levels were elevated with advancing age, and radiation effects were observed for both parameters.

A number of immunological studies on the AHS subjects have been conducted in which age-related changes were also investigated. Studies on the detection and characterization of immature T cells revealed a statistically significant age-dependent increase in CD3^-4^ (CD8^+) T cells in peripheral blood. This age-related increase in frequency might be causally related to an age-dependent decrease in T-cell function. B cells showed a similar reduction in function with age as was observed in T cells, however, no significant effect of radiation exposure on B-cell frequency was observed. In contrast to the findings demonstrated in T and B cells, the absolute number of natural killer (NK) cells in peripheral blood was found to be significantly increased with age. Both NK- and antibody-dependent cell-mediated cytotoxicity activities also demonstrated significant increases with age. Despite the dramatic changes in NK cell number with age, no significant radiation effects on NK cells have been demonstrated.

Four types of mutation assays have been conducted at RERF primarily as biological dosimeters to evaluate radiation exposure. These assays have shown that the annual increment of average mutation frequency was one order of magnitude greater in the T-cell receptor gene complex and HLA-A2 mutations. Such a wide difference was considered to be related to the genes, structures and functions. Each assay indicated an age-related increase in the spontaneous mutation rate, and radiation effects were suggested in mutation rates of T-lymphocyte hypoxanthine guanine phosphoribosyl transferase (HPRT) and T-cell receptors (TCR).

In the course of long-term cytogenetic surveys searching for somatic effects of radiation, some evidence has been found for age-associated changes in lymphocyte chromosomes of the survivors. The mitotic index in 2-day-old cultures of cells grown in the presence of phytohemagglutinin (PHA) tended to decrease with age. This decrease was not influenced by other factors including radiation dose. Analysis of the frequency of aneuploid cells – aneuploidy is defined as the loss or gain of a certain chromosome in a cell due to mitotic errors – has revealed a tendency for the X chromosomes in females and the Y chromosomes in males to be lost with increasing age. However, no radiation dose effects were observed.

**Tissue Changes and Disease**

Tissue changes and diseases of interest in aging studies at ABCC-RERF are shown in Table 4. Most of the conditions are degenerative diseases or degenerative lesions that are positively correlated with age. The prevalence of lenticular opacities, as determined by precise ophthalmological study, and of refractory anemia both increased with age, and there is good evidence of radiation effects on both. Although the relationship between these diseases and
aging is quite apparent, the relationship may be considered to be a specific effect of radiation rather than an indication of radiation-accelerated aging. In the sixth report of the AHS, it was first demonstrated that the prevalence of arteriosclerosis based on X-ray findings was related to radiation dose\textsuperscript{67}. Both stroke and coronary heart disease are typical age-related diseases in which sclerotic change of the arteries plays a major pathogenic role. Both of these diseases are significantly more prevalent in highly irradiated women from Hiroshima\textsuperscript{93,94}. These increases remain even when possible biases in case detection are taken into account. Furthermore, a reanalysis of these incidence data with the observation period extended up to 1984 suggests a positive radiation effect in women from both cities. However, more precise analyses will be needed to confirm these results.

### DISCUSSION

In the 15 years since the comprehensive review of aging among the AHS cohort by Finch
and Beebe\textsuperscript{34}, the hypothesis that exposure to ionizing radiation accelerates the natural processes of aging has been investigated in the population of A-bomb survivors at ABCC-RERF by means of clinical, epidemiological, and laboratory techniques. To date, these studies have not clearly shown that radiation has such an effect, although abundant data have been accumulated to test this hypothesis. Extending the observation period of the LSS cohort for mortality up to 1978 did not change the result that shortened life expectancy seen in this population was associated not with any nonspecific cause, but with cancer\textsuperscript{54,55}. There are still marked contrasts between these LSS data and the data on the occupational exposure of U.S. radiologists, for whom excess deaths from causes other than cancer were also suggested\textsuperscript{30}. The interpretation of the differences between the two groups is difficult, but the nature of the radiation exposure in each group differs, and confounding factors other than radiation have been noted for the population of radiologists studied. However, it seems reasonable and important to continue our observations of mortality trends among the A-bomb survivors and to reanalyse the data to test again the hypothesis, as there have been relatively few deaths in the younger age groups, for whom the most pronounced putative effects might be expected.

A broad spectrum of parameters of aging have been studied over the past 15 years in the AHS population and the results are still essentially negative. Some of the aging parameters, however, show positive or equivocal effects for radiation. In their so-called “physiological age” study, in which they intended to create an index to express an individual’s progression in the aging process, Belsky et al. could not find any relationship between radiation dose and the overall index of physiological age. However, grip strength and audiometry, both of which were used in calculations of physiological age because they decreased significantly with age, varied between the higher dose and control groups\textsuperscript{63}. In addition, borderline type of glucose tolerance was more frequent with age\textsuperscript{70}. These results may give support to the hypothesis to the acceleration of natural aging due to radiation, but the observed radiation effects were restricted to only a few age or dose groups. For example, the blood sedimentation rate and some fraction of serum protein levels were elevated with age, and this elevation was more apparent in heavily exposed subjects; however, the cause of these effects is still unknown\textsuperscript{71,72}.

In studies of immunological changes among A-bomb survivors at RERF, serum anti-EB titers, PHA response, and mixed lymphocyte culture response showed equivocal radiation effects. Furthermore, somatic mutation studies on T-lymphocyte HPRT and TCR have demonstrated an interesting effect: The frequency of mutation shown by these indices increases with age and also with radiation dose\textsuperscript{84,86,87}. These findings may also support our hypothesis, but further investigation will be necessary, as these indices are reliably related to radiation and there is some probability that they might be better understood as specific effects of radiation rather than as nonspecific effects of radiation on aging. The effect of radiation on lenticular opacities and refractory anemia will also be included in the same category of index.

Atherosclerosis is one of the most common age-related pathological phenomena and it is considered a good marker of aging, as diseases based on atherosclerosis are a major cause of death in older age groups. It is noteworthy that radiation effects were suggested in some of the clinical manifestations related to atherosclerosis, such as the incidence of stroke and coronary heart disease, and the frequency of atherosclerotic lesion, which was usually diagnosed as
calcification of the aorta by means of chest X rays\textsuperscript{66,93,94}.

There are several approaches to clarifying the aging process in humans. In the area of epidemiological or clinical gerontological research, attempts to develop useful indices of aging essentially use measurements thought to be related to the aging process itself or closely related to chronological age. With its 30-year, biennially updated database based on the AHS medical examinations, RERF is uniquely able to use an abundance of disease incidence, death information, laboratory, and physiometric data to portray the lifetime physiological and pathological history of 20,000 AHS participants. Examination of the age-specific incidence rates in the AHS data readily reveals which diseases are more closely associated with the aging process: Coronary heart disease, cataract, senile dementia, and osteoporosis all increase steadily in a monotonic relationship with chronological age.

When considering analyses using these accumulated data, however, it is important to differentiate between age effects and cohort effects\textsuperscript{100}. For example, an impression of an overall increasing trend in disease incidence with age could arise as an artifact of a difference in cohort response mainly due to a change in environmental conditions. When appropriately stratified by birth cohort or other factors, the trend may or may not be changed. A typical example of such a phenomenon is seen in vertebral fracture incidence, which appears to increase with age in both genders. However, when the incidence is shown by 10-year birth cohorts, a completely different view emerges. It is immediately recognized that there are significant differences in incidence between birth cohorts even at the same attained age, and there is no increase in the incidence for males over the follow-up period\textsuperscript{98} (Figure 1).

The lifetime pattern of change in certain physiological variables such as systolic and diastolic

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Incidence rate of thoracic vertebral fractures by birth cohort (Ref. 98).}
\end{figure}
blood pressure, heart rate, and total serum cholesterol can also be examined using the AHS data, thus providing another unique view of the aging process. The primary advantage of cross-sectional studies is that the presence of an age trend for a parameter in a population can be detected easily. Caution is necessary in interpreting such results, however, since differences among age groups include birth-cohort effects as well as age effects. Thus, as in the case of disease incidence, age and cohort effects may be confounded. Yet this can be avoided by using serial measurements of the same individuals and by using appropriate statistical analyses such as the "growth curve" technique for longitudinal data. An analysis of long-term data in the AHS database using the growth curve technique is now in progress. How much and to what degree ionizing radiation modifies or influences the natural courses of change of physiological variables with age would be the key question of such an analysis. There may be some confounding factors influencing the association between radiation and age-related changes of physiological parameters. Possible confounders can easily be incorporated into the analysis, as useful information about lifestyle including alcohol consumption, dietary habits, smoking, parity, and occupation has been collected in the AHS medical examinations.

The overall results of studies conducted on the AHS population over the past 15 years to test the hypothesis that ionizing radiation accelerates natural aging seem to have been inconsistent or rather negative. However, some preliminary results have shown a suggestive increase in atherosclerotic diseases and accelerated aging in the T cell-related immune system due to exposure to radiation. Since these observations may prove relevant to future studies of late radiation effects, possibly using new gerontological study techniques, and since the subjects exposed at relatively young ages are approaching the ages of which they will suffer from age-related diseases, aging studies on the A-bomb survivors should continue. Potentially fruitful measures of body functions conducted in the past could be repeated in the same subjects to look for longitudinal variation, perhaps with more advanced techniques, should they become available. Fresh approaches on the molecular or submicroscopic levels could likewise break new ground in the search for aging phenomena.

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