Aging in Hiroshima and Nagasaki Atomic Bomb Survivors

Speculations Based upon the Age-Specific Mortality of Persons with Malignant Neoplasms

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Evaluation of 1639 malignant tumors from 3067 autopsies of members of the Extended Life Span Study Sample reveals that death occurs earlier in those persons most heavily irradiated (≥100 rad) compared with those persons who were less exposed. This effect is particularly pronounced in the younger age categories and among females and is not attributable to a specific neoplasm. Assuming that a positive correlation exists between aging and the age-specific mortality of persons with neoplasms, it is concluded that this response is consistent with other observations which suggest the presence of accelerated or precocious aging in the most heavily irradiated group of survivors (Am J Pathol 75:1-12, 1974).

Two of the more conspicuous experimental consequences of exposure to biologically significant amounts of ionizing radiation are a reduction in life span and an increased prevalence of many types of tumors. These phenomena are interrelated experimentally in that


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the prevalence and appearance time of neoplasms have been shown to represent excellent parameters of the accelerated or precocious aging noted postexposure.\textsuperscript{1-2} In this regard, however, it is important to emphasize that the life-shortening response to radiation is not entirely dependent upon the tumorigenic effect. Thus, in an elaborate evaluation of a large number of mice exposed to neutrons and gamma rays from an atomic weapon exploded near Eniwetok, Upton \textit{et al}\textsuperscript{3} noted that the attendant reduction in longevity was not attributable to an increased mortality from one or several specific entities but rather correlated with the premature appearance of all of the diseases associated with spontaneous senescence. An increased prevalence of several malignant tumors has been documented among the atomic bomb survivors of Hiroshima and Nagasaki. Implicated thus far are: several forms of leukemia, myelofibrosis with myeloid metaplasia, malignant lymphoma including multiple myeloma in Hiroshima survivors, carcinoma of the thyroid, possibly carcinoma of the lung, carcinoma of the major salivary glands, possibly carcinoma of the breast, and a variety of malignant tumors among individuals exposed during the initial decade of life.\textsuperscript{4,5} In several of the foregoing instances, the appearance time (the period between exposure and the onset of the malignancy) has also been accelerated in proximally located persons in comparison with a more distal group or with individuals who were away from the involved cities at the time of the explosions.

The purpose of the present study is to extend the above observations to include an evaluation of all neoplasms, as documented by postmortem examination, as a function of exposure status and age at death among the survivors of the atomic bombs of Hiroshima and Nagasaki. As such, it represents one of a series of efforts to apply various aging parameters to the populations under surveillance at the Atomic Bomb Casualty Commission (ABCC) even though the authors realize that age-specific mortality associated with tumors is not universally accepted as a measure of aging.

\textbf{Materials and Methods}

Three thousand sixty-seven (3067) members of the Life Span Study Sample autopsied prior to 1968 form the basis of this study. The composition of the total Life Span Study Sample by exposure status, age at the time of exposure and sex is summarized in Table 1 and Text-figure 1. Other demographic characteristics of this carefully constructed population are detailed elsewhere.\textsuperscript{6,7} In recent years, ABCC autopsy contractors have achieved a 47\% autopsy rate among hospital deaths and a 32\% rate among persons who died at home. In this connection, several areas of possi-
Table 1—Approximate Composition of Life Span Study Sample

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Distance from hypocenter (m)</th>
<th>Hiroshima</th>
<th>Nagasaki</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner proximal</td>
<td>0-1,999</td>
<td>21,200</td>
<td>6,600</td>
<td>27,800</td>
</tr>
<tr>
<td>Outer proximal</td>
<td>2,000-2,499</td>
<td>11,500</td>
<td>5,100</td>
<td>16,600</td>
</tr>
<tr>
<td>Distal</td>
<td>2,500-10,000</td>
<td>21,200</td>
<td>6,600</td>
<td>27,800</td>
</tr>
<tr>
<td>Not in city</td>
<td></td>
<td>21,200</td>
<td>6,600</td>
<td>27,800</td>
</tr>
<tr>
<td>Total persons</td>
<td></td>
<td>75,100</td>
<td>24,900</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Autopsies are performed in meticulous fashion and are generally reviewed by two or more pathologists. Disease entities are coded in standard fashion. Instances where a malignant neoplasm is included as the primary or contributory cause of death are included herein. Also included are cases in which a malignant tumor, with the cell type documented histologically, was removed surgically prior to death with the latter attributable to a nonneoplastic etiology.

Exposure categories are based upon Tentative 1965 Dose (T65D) Estimates provided by Oak Ridge and are thought to be reasonably accurate. These estimates are based upon the air dose curves shown in Text-figure 2 with appropriate corrections for man-made and natural objects. On the basis of the foregoing, individuals are grouped into the following exposure categories by total dose estimate with gamma rays and neutrons combined on a 1:1 basis: 1) 100 or more rad; 2) 1 to 99 rad; 3) Less than 1 rad. The latter category includes persons who were away from the

TEXT-FIG 1—Survivors by age, 1950 census, Hiroshima vs. Nagasaki.
Table 2—Demographic Composition of Autopsy Sample*

<table>
<thead>
<tr>
<th>Age at death (yrs)</th>
<th>&lt;1</th>
<th>1-99</th>
<th>≥100</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>0-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>9</td>
<td>23</td>
<td>7</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>30-39</td>
<td>26</td>
<td>32</td>
<td>20</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>40-49</td>
<td>42</td>
<td>24</td>
<td>39</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>50-59</td>
<td>111</td>
<td>101</td>
<td>74</td>
<td>56</td>
<td>13</td>
</tr>
<tr>
<td>60-69</td>
<td>179</td>
<td>303</td>
<td>145</td>
<td>165</td>
<td>16</td>
</tr>
<tr>
<td>70-79</td>
<td>220</td>
<td>237</td>
<td>191</td>
<td>211</td>
<td>22</td>
</tr>
<tr>
<td>80-89</td>
<td>141</td>
<td>101</td>
<td>115</td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>90-99</td>
<td>22</td>
<td>12</td>
<td>10</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>754</td>
<td>838</td>
<td>603</td>
<td>589</td>
<td>86</td>
</tr>
</tbody>
</table>

* Figures indicate actual number of persons in group; individuals away from cities at time of bombings included in <1 rad group.

two cities at the time of the explosions. Parenthetically, it should be noted that approximately 50% of the Life Span Study Sample (Table 1) was exposed to less than 1 rad at the time of the bombings.

Results

The autopsy prevalence of malignant tumors as a function of exposure category is shown in Text-figure 3. A few specific entities of general interest are included separately as well as the totals for all neoplasms.
For persons with more than one primary neoplasm, each malignancy is included separately. This point deserves emphasis since such an approach appears to exaggerate the prevalence of malignant tumors (i.e., it is not the case that 66% of persons autopsied at ABCC die with malignant neoplasms). As might be expected, an excess number of malignancies is noted in the \( \geq 100 \) rad group. The most pronounced relative increase is noted with leukemia.

Age at death for autopsied persons with malignant neoplasms as a function of exposure category is shown in Text-figure 4. The age-specific mortality is displaced to the left (i.e., younger age at death) for both sexes in the \( \geq 100 \) exposure category. This effect is particularly evident in the younger age groups and is more pronounced in females than in males.

Carcinoma of the stomach is the most frequently encountered malignant neoplasm among the general Japanese population; Japan ranks second only to Finland with respect to the number of deaths attributable to this entity. Although the incidence of this neoplasm does not appear to be increased postexposure in the surviving population (Text-figure 3), the relative frequency of carcinoma of the stomach is so pronounced in most age increments that a positive relationship between the age at death and exposure status could be responsible for the discrepancies noted in Text-figure 4. Therefore, the
attendant data are replotted in Text-figure 5 excluding the 359 examples of this disease. It is evident that this maneuver does not abolish the effect noted in Text-figure 4.

Carcinoma of the thyroid is also relatively frequent in Japan, particularly among autopsy populations when specific surveillance mechanisms are instituted to document occult tumors as is the case at ABCC.
Text-figure 6—Cumulative mortality of persons with malignant neoplasms excluding carcinoma of thyroid by exposure category as a function of decade of death.

Text-figure 6 depicts the data excluding the 536 examples of this entity. Again, the displacement under consideration persists.

Since the discrepancies in appearance time are most pronounced in the younger age categories, tumors peculiar to this period might be expected to be of particular importance in the genesis of these differences. As shown in Text-figures 7 and 8, such is partially the case. Exclusion of leukemia markedly mutes the effect in autopsied males, although not in females, and exclusion of both leukemia and carcinoma

Text-figure 7—Cumulative mortality of persons with malignant neoplasms excluding leukemia by exposure category as a function of decade of death.
of the thyroid virtually abolishes this response among the autopsied male although it persists in the female component.

Discussion

Whole body exposure of several types of rodents to moderate amounts of ionizing radiation occasions a shortened survival in comparison with their nonirradiated contemporaries. This response is dose-dependent and cannot be attributed to a specific cause. The exposed animals appear to die at an earlier age from most of the same disease entities which afflict their nonexposed counterparts. Such accelerated or precocious aging, although generally accepted with respect to experimental animals, has yet to be documented conclusively in man. Thus, to date, the only positive evidence relates to the radium dial painters, the early American radiologists and possibly the exposed populations of Hiroshima and Nagasaki. The attendant data are discussed in detail elsewhere. Two important studies relevant to the ABCC experience may be summarized as follows:

1) Mortality ratios for survivors located within 1400 meters of the hypocenter at the time of the explosions were higher during 1950–60 than the comparable figures for more distally located persons. The excess in mortality was attributable to a variety of causes, was particularly pronounced during 1950 to 1952 and gradually became less marked subsequent to that time. In addition, the average radiation dose estimates were significantly larger for those individuals.
who died of natural causes during this decade than for those who survived the interval.

2) In a somewhat similar approach, Ciocco subsequently focused attention upon those individuals who were 45 years of age or older at the time of the explosions as that portion of the Life Span Study Sample subject to the greatest mortality risk as well as a group which, at the time of the evaluation (1965), was rapidly approaching the modal age of death. Ciocco documented similar differences in mortality which were particularly pronounced during 1950 to 1955 and in the female segment of the population where they were significant at the 2% level.

The present study documents a displacement in the age-specific mortality curve to a younger age at death from malignant neoplasms for autopsied survivors exposed to an estimated dose in excess of 99 rad. As in the two related ABCC studies summarized above, this effect is more pronounced among females. Of interest in this regard, female mice have been shown by several investigators to be more susceptible than males to the life-shortening effects of radiation. In this connection, however, it should be reemphasized that not all observers accept age-specific mortality associated with neoplasia as a parameter of aging. Assuming for the moment, however, that a positive correlation does indeed exist, it is tempting to postulate that the segment of the exposed population susceptible to the tumorigenic effects of radiation is also particularly sensitive to the life-shortening effects. A possible common denominator between these two responses could involve the defined mutagenic effect of ionizing radiation. Somatic mutation has been implicated in several of the currently popular theories of aging.

The mortality data of Jablon et al and Ciocco suggest an effect which was most pronounced in the early 1950's. In contrast, the vast majority of autopsies on members of the Life Span Study Sample have been performed since the inauguration of the current Pathology Study Program in 1961. Therefore, assuming a positive correlation between aging and the age-specific mortality of individuals with neoplasms, and neglecting for the moment the observation that the autopsy series does not identically reflect events which encompass the entire Life Span Study Sample (see below), accelerated or precocious aging among individuals receiving the heaviest radiation would appear to continue through the 1960's and probably to date. In fact, the unusual prevalence of a variety of neoplasms among children who were less
than 10 years of age when they were exposed to 100 rad or more, a phenomenon which has yet to reach a peak, suggests that an accentuation of the accelerated aging demonstrated herein will become evident during the next several years.

As emphasized previously, several important discrepancies distinguish members of the Life Span Study Sample who are autopsied vs. those who are not: the very young and the very old are underrepresented in the postmortem group as are individuals who succumb attendant to trauma; on the other hand, persons with suspected malignancies, particularly leukemia and related disorders, appear to be overrepresented. Presumably such bias does not influence the differences between exposure groups described herein but still should serve to exert a measure of caution when extrapolating from the autopsy segment of the Life Span Study Sample to all deceased members of this population. Why not employ the latter group for the present study? Here the problem of bias is more marked in that the degree of correlation between the death certificate diagnosis and the postmortem findings varies considerably according to the malignancy in question.

Also of importance in the present context is the study of Johnson et al which included an evaluation of skin tumors among a subpopulation of the Life Span Study Sample. This subpopulation is known as the Adult Health Study Sample and is examined at 2-year intervals for clinical abnormalities. In an evaluation of 12,007 persons, Johnson et al documented an increased prevalence of select benign skin tumors among proximally exposed persons in comparison with their more distally located counterparts and also noted an earlier average appearance time of such lesions in the former group. This study, among a more representative subset of the Life Span Study Sample, thus appears to support the observations reported herein.

As implied above, younger individuals have been noted to be particularly sensitive to the tumorigenic effects of radiation in several ABCC studies. In this connection, displacement of life span following a constant amount of radiation in the experimental situation is generally inversely proportional to the age at exposure. Therefore, it is of interest in the present study to note that the most marked changes in the mortality data are associated with the younger age groups.

References