UR-598

UR-598

AEC RESEARCH AND
DEVELOPMENT REPORT

CONCEPT AND CRITERIA OF RADIOLOGIC AGING

by

George W. Casarett

THE UNIVERSITY OF ROCHESTER
ATOMIC ENERGY PROJECT
ROCHESTER, NEW YORK

LEGAL NOTICE

This report was prepared as an account of Government sponsored work. Neither the United States, nor the Commission, nor any person acting on behalf of the Commission:

A. Makes any warranty or representation, expressed or implied, with respect to the accuracy, completeness, or usefulness of the information contained in this report, or that the use of any information, apparatus, method, or process disclosed in this report may not infringe privately owned rights; or

B. Assumes any liabilities with respect to the use of, or for damages resulting from the use of any information, apparatus, method, or process disclosed in this report.

As used in the above, "person acting on behalf of the Commission" includes any employee or contractor of the Commission, or employee of such contractor, to the extent that such employee or contractor of the Commission, or employee of such contractor prepares, disseminates, or provides access to, any information pursuant to his employment or contract with the Commission, or his employment with such contractor.

UR-598

UC-48:
Biology and Medicine
TID-4500, (16th Ed.)

THE UNIVERSITY OF ROCHESTER
Atomic Energy Project
P. O. Box 287, Station 3
Rochester 20, New York

* * *

Contract W-7401-eng-49 between the U. S. Atomic Energy Commission and the University of Rochester, administered by the Department of Radiation Biology of the School of Medicine and Dentistry.

CONCEPT AND CRITERIA OF RADIOLOGIC AGING

by

George W. Casarett

Division: Radiology and Biophysics

Division Head: William F. Bale

Section: Radiation Tolerance

Section Head: J. B. Hursh

Date Completed: 6/16/61

Date of Issue: 8/1/61

CONCEPT AND CRITERIA OF RADIOLOGIC AGING

By

George W. Casarett

ABSTRACT

Critical general comparison of various manifestations of aging and late radiation effects strongly suggests premature aging as an effect of irradiation, on a generalized or localized basis. Presented is an hypothesis of the process of "radiologic aging" at the tissue level, based on histopathologic studies of the development of manifestations of aging and of late radiation effects in tissues prior to disease development. This hypothesis maintains that nonspecific injury of endothelium of fine vasculature by direct or indirect mechanisms leads to increase in density and amount of collagenous substance interstitially and in subendothelial regions of arterioles. These changes constitute a temporal advancement in the increase of the histohematic barrier and in the development of arteriolocapillary fibrosis, which are progressive processes in "normal" aging. Eventually these processes cause progressive reduction in number of dependent parenchymal cells due to relative hypoxia and malnutrition. Secondary to parenchymal loss is a process of replacement fibrosis and reduction of fine vasculature, with consequent further increase in histohematic barrier and arteriolocapillary fibrosis. Concomitant with parenchymal loss is progressive reduction of functional reserve capacities and a corresponding progressive increase in susceptibility of tissues to trauma, stress, and disease.

CONCEPT AND CRITERIA OF RADIOLOGIC AGING

By

George W. Casarett

Although it is not yet possible to define and compare the essential processes of aging and of late radiation effects, their late manifestations can be compared.

The manifestations of aging in adult mammals comprise a progressive deterioration of tissues, with concomitant decline of functional reserves and adaptive powers, which leads eventually to disease and inevitably to death.

Aging is not uniform with increasing time, but varies in rate among individuals and among organs of an individual. The rate of aging, the development of disease, and the life span are the net results of many variable, modifying, conditioning and correlating forces, both environmental and inherent, including genetic constitution. The integration of these forces determines the physical status of the aging individual.

There are four general types of data which are often used as criteria of alteration of aging process by irradiation. These are: data pertaining to mortality, pathology and disease incidence, subclinical histopathology, and physiology (including biochemistry). It is fruitful to examine these criteria critically in relation to one another, in a general manner, to determine their relative usefulness with respect to assessment of aging process.

According to ideal concepts, an agent is regarded as causing premature aging if it causes the force of age-dependent mortality to increase earlier in the treated than in the nontreated control population, brings forward in

time the age of onset of diseases which affect the controls, without altering the sequence or the incidence of diseases and causes of death, and causes characteristic morphologic and physiologic manifestations of the aging process to appear and develop at proportionately earlier chronologic ages.

If the agent causes these manifestations to develop prematurely, but does not alter their rate of development thereafter, the effect is simply one of precocious aging. If the agent causes also an increase in rats of development of the manifestations, the effect is not simply precocious but one of acceleration of aging.

1. Mortality Data

With increasing age in the adult there is generally a progressive increase in the probability of disease and accident and in the probability of death.

Inherited body constitution establishes essentially the baseline in an individual with respect to the aging process and its rats and the maximal life span even under optimal conditions.

However, a comparison of mean or median longevities alone is meaningless in terms of the process or rate of aging, since many age-independent factors are capable of reducing or increasing the median or mean life span of a population. Comparison of the temporal distribution of death is a little more meaningful but still very limited in usefulness with respect to assessment of aging process.

For a group of mammals maintained under excellent environmental conditions the shape of the arithmetic survival or mortality curve tends toward the rectangular (Figure 1.A.), indicating a relatively low incidence of age-independent causes of death. At the other extreme, a group of mammals kept

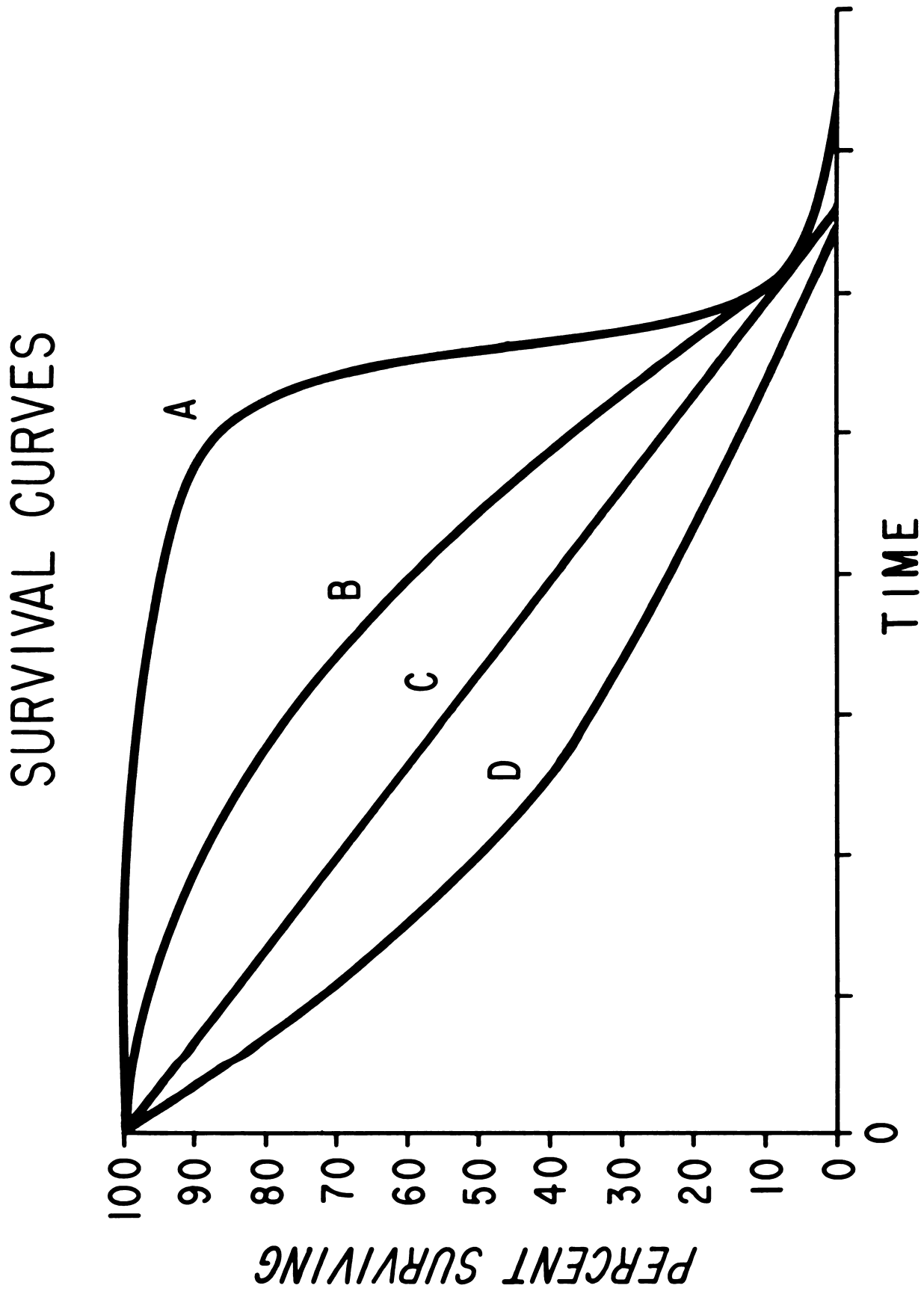

Figure 1. Survival Curves.

under poor environmental conditions and subject to a very high incidence of age-independent causes of death, with few living to senescence, exhibits an arithmetic survival curve which resembles a logarithmic decay curve, (Figure 1.D.). When multiple life-shortening factors independent of age modify an arithmetic rectangular survival curve they tend to reduce it in the direction of a straight line (Figure 1. B and C) or, if the effect is marked, toward the logarithmic decay curve [1].

Combinations of the effects of premature aging and of increases or decreases in incidence of age-independent causes of death at various times in the life span can result in survival curves of many shapes. Furthermore, when an agent is capable of producing a prophylactic or therapeutic effect in relation to any serious age-independent or age-dependent disease in a population, this can result in change in survival curves and even in increased aftersurvival. On the other hand, an activating effect on pre-existing chronic or latent infectious disease can alter survival curves in other ways. The most that can properly be said of a survival or mortality curve is that it is compatible or incompatible with a supposed process [1].

It is well established experimentally in mammals that exposure of the whole-body or parts of the body to ionizing radiation in substantial but sublethal doses can shorten life span. Numerous mathematical analyses and interpretations of such data have been performed in relation to the aging problem [2-8]. In the case of partial-body exposure, the life shortening effect is variable in degree, depending on the kind and amount of tissue irradiated as well as the dose [3].

The observation of radiation life shortening, the reduced radiation LD_{50} of irradiated groups as compared with their nonirradiated controls of the same chronologic age, and the residual tissue damage and delayed effects of irradiation, all indicate that some of the radiation injury or its consequent damage is irreparable.

According to Blair's theory of radiologic life shortening[2], the injury of aging and the irreparable injury of irradiation are additive in producing or contributing to radiation lethality, and the irreparable component of the injury is equivalent to premature aging (at least in an actuarial sense), in that it ultimately deprives the animal of part of its expected life span.

Limited experimental observations in this laboratory suggest that irreparable injury is detectable, after an interval of maximal tissue recovery, as a reduction in acute lethal dose, and that the LD_{50} dose for irradiation decreases with increasing age[9]. Limited experimental experience with measurement of irreparable injury by decrement in radiation LD_{50} at various times after brief total-body irradiation suggests the possibility that the irreparable radiation injury may remain more or less constant, in comparison with nonirradiated animals of the same age, at least until the point in time when age-dependent diseases increase considerably in incidence prior to this occurrence in the nonirradiated population[9] (Figure 2). After this time it seems probable there may be greater differences in LD_{50} between the two groups when compared at the same chronologic ages, but perhaps not when compared at the median death times.

If these observations prove to be true, and if it is true also that the irreparable injury of irradiation is equivalent to aging injury in an actuarial sense, then in the absence of any effect of the irradiation on the

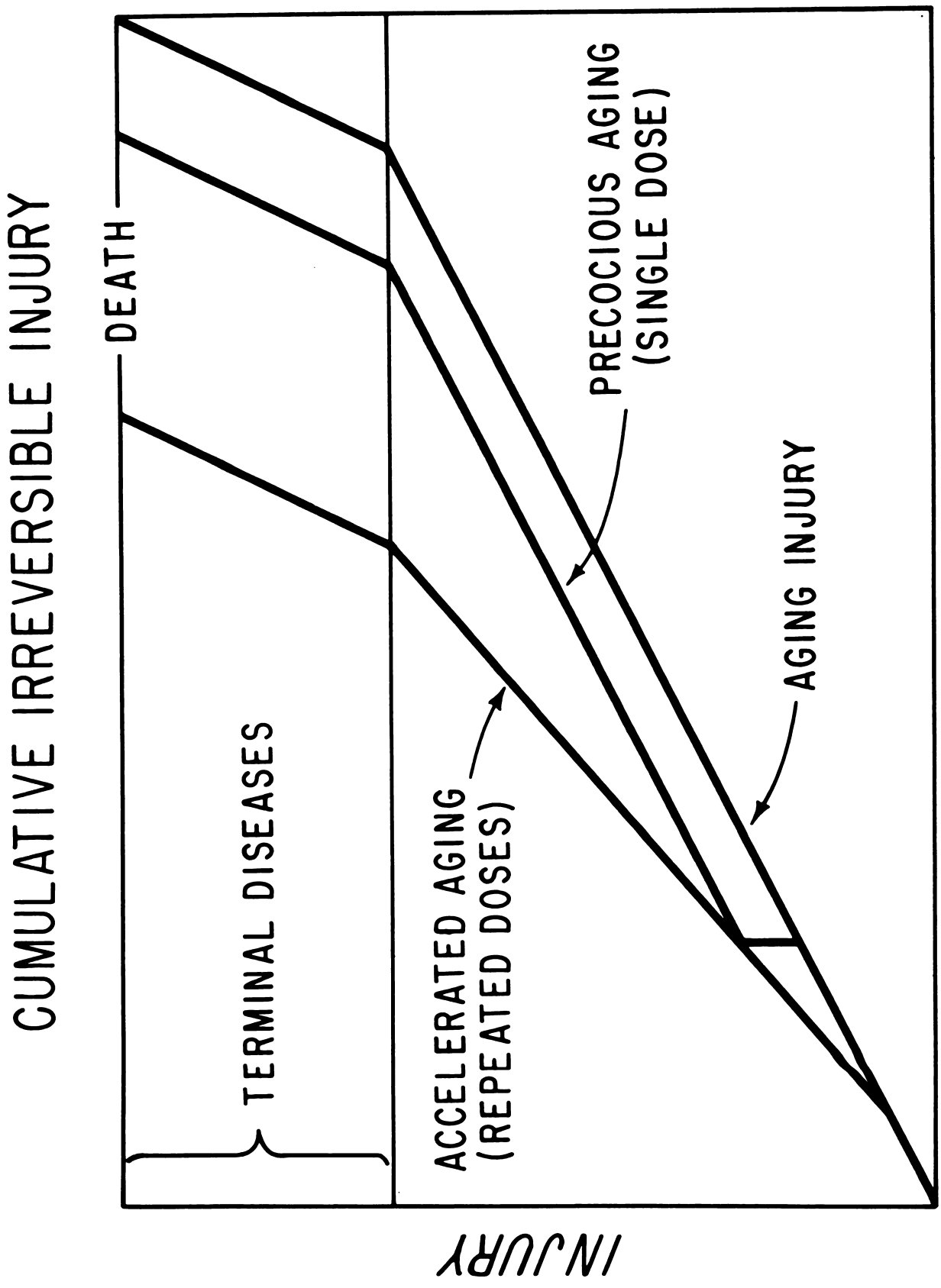

Figure 2. Cumulative Irreversible Injury.

incidence and distribution of age-independent causes of death it may be expected that a brief total-body life-shortening radiation exposure would result in a survival curve which is similar in shape or slope to the control curve, but displaced to an earlier time period in a manner compatible with the concept of precocious aging.

This seems to be the case often in single-dose experiments. However, sometimes the arithmetic survival curves of briefly irradiated groups become flattened and must be considered compatible with either the concept of accelerated aging or of increased incidence of age-independent mortality or a combination of precocious aging and increase in age-independent mortality.

On the other hand, protracted irradiation, e. g., daily or weekly irradiation with substantial doses for a long period of time, may involve the accumulation of irreparable injury in a manner such that there would be increase in the slope of a plot representing irreparable injury with passing time, as compared with the simple persistence of a constant amount of irreparable injury following a brief exposure (Figure 2). However, under these conditions of exposure, the injury picture is complicated by the constant production or existence of unrepaired injury of reparable types as long as irradiation is continued and is probably different in animals irradiated until their death as compared with animals whose irradiation is stopped far short of death. In either case the unrepaired injury of reparable types may alter the susceptibility of the animals to age-independent or age-dependent causes of death, the direction and extent depending upon the dose rate, changing tissue sensitivity, and the balance between injury and recovery rates.

If there is accumulation of irreparable injury with long protracted

or repeated irradiation it may be expected such exposure may result in a survival curve for experimental animals which is steeper in slope than the control curve, i. e., a curve compatible with either the concept of accelerated aging or increased incidence of age-independent causes of death or a combination of the two. This is sometimes the case in protracted-exposure experiments. However, in other instances the survival curves have been similar in shape to the control curves, but simply advanced in time, compatible with the concept of simple precocious aging. This latter finding has led some investigators (7) to the interpretation that at comparatively low daily dose rates, shortening of life span may be determined mainly by the irradiation received during the early part of the life span.

From these general considerations it can be seen that mortality data alone are greatly limited as criteria of effect of total-body irradiation on the aging process. Such data are even more limited in their usefulness for this purpose for partial-body irradiation, as from internally administered radioactive isotopes.

2. Pathology and Disease Incidence

Survival curves coupled with data on the incidence and temporal distribution of diseases and causes of death are more enlightening. However, in order to bring such data to bear on the aging process, there must be knowledge of the relative age-dependence of the causes of death, including recognition of the hereditary susceptibilities to causes of death which are more or less age-dependent or age-independent.

A well-kept aging population of genetically heterogeneous animals tends to die as a result of a relatively wide variety of age-dependent causes of death. Many highly inbred or genetically more homogeneous aging populations

of animals tend to show a lesser variety of causes of death and usually high incidence of certain specific causes of death for which they have a strong genetic susceptibility. In general, the age-dependent diseases or the so-called diseases of aging are essentially either degenerative or neoplastic in character, and it is well known that many of the neoplastic diseases develop in relation to previously developing degenerative tissue states either at the site of origin of the neoplasms or in some physiologically related tissue.

As in the case of aging manifestations, the propensity for development of diseases is not uniform with respect to individuals of a population or organs of an individual. Some diseases are more or less progressively age-dependent. Other age-dependent diseases show considerable age-specific propensity, the incidence rising rapidly to a peak at certain ages and then declining rapidly after those individuals with a genetic tendency for the disease have died.

In order to establish a baseline for interpretation of aging process by means of data on disease incidence or cause of death it is necessary to know the age-dependent diseases in a well-kept aging population, and to recognize the possibility that diseases or causes of death which are relatively age-independent, whether they be infectious diseases or degenerative or neoplastic diseases for which there is very strong genetic propensity, may be extraordinarily increased in incidence or time of onset by relatively little tissue injury, relatively independent of change in aging process. It is necessary to recognize that increased or decreased incidence of age-independent causes of death may change, in relative fashion, the age-specific incidence of age-dependent diseases expected in an undisturbed control popu-

lation. Furthermore, for a better understanding of the disease picture in relation to aging process, it is necessary to be able to distinguish between temporal advancement of disease and true induction of disease.

If an agent results in the earlier appearance of a disease in a population, with increase in age-specific incidence at earlier ages and without a significant increase in absolute or life-time incidence, as compared with controls in a well-kept aging population, then the disease may be regarded as having been temporally advanced by the agent. When the agent results in a considerable increase in absolute incidence of a disease as compared with the incidence expected within the maximal life span of the species or strain, then the excess incidence of the diseases may be regarded as having been induced by the agent.

It is well known, however, that the observed mean life spans of experimental animal populations often fall far short of their potential averages because infectious diseases kill or damage large numbers of individuals well before the senescent period of life. Some age-dependent diseases of long latency may rarely or never develop spontaneously within the observed life span in many individual experiments. Consequently, it is possible in some instances that some of the diseases regarded as induced by the experimental treatment under these circumstances may have been instead diseases of relatively long latency with their time of onset greatly advanced temporally in individuals with some propensity for them.

The involvement of alteration of aging process in effects of total-body irradiation on life span is often judged according to ideal standards and assumptions which may not be true. Shortening of life by total-body irradiation is conceded to be an effect of premature aging only if there

is no induction of disease and if there is a proportionately equal temporal advancement of all diseases common to the species or strain. In practice this ideal concept implies, among other assumptions, the assumptions that all of the diseases in question are age-dependent to the same degree, that all of the diseases and causes of death under conditions of maximal longevity are known, that the irradiation is always applied uniformly throughout the tissues, and that the irradiation, if it alters the degree or rate of aging at all, must alter the relative rates of aging process in various parts of the body to a degree proportionate to their relative rates of aging in non-treated animals. The truth of this latter assumption depends greatly on the fundamental nature of the aging process, which, of course, is not yet known.

In the case of total-body irradiation experiments on rats and mice, some experiments, especially among those with single dose exposures shortening life with a simple temporal displacement of the survival curve, have shown approximately the same diseases in approximately the same incidence in irradiated and control groups (2), i. e., a simple temporal advancement of disease. Other such experiments have shown about the same diseases, although not necessarily in the same incidence. Still other experiments have shown, in addition to advancement of certain diseases, a considerable induction of certain other diseases. This induction tends to occur more often in inbred strains with a high genetic susceptibility to certain diseases, e. g., leukemia or ovarian tumor in certain inbred strains of mice.

The observed strain variation in life shortening in irradiated mice can be partially attributed to genetic differences in the sensitivity to the leukemogenic effects of irradiation (10). When leukemia mortality is excluded, life shortening due to all other causes is found to vary compara-

tively little between strains.

In the case of total-body irradiation of genetically more heterogeneous animal populations usually the temporal advancement of disease is relatively of greater importance in life shortening than induction of disease, while in the case of highly localized irradiation, particularly with the use of the more intense or larger doses possible to administer without acute lethality, induction of disease at the site of irradiation or indirectly in a physiologically related site, is relatively of greater importance.

Intensive highly localized irradiation, as with internal radioisotopes which concentrate in certain tissues, enhances greatly the tendency to diseases related to the part irradiated, with relatively less enhancement of the tendency to disease development in unrelated parts of the body. Whether we regard these radiation-linked diseases as induced or temporally advanced, the incidence depends greatly on the latent periods for these diseases in relation to the temporal proximity of development of other terminal diseases common to the species or strain in other parts of the body. This, in turn, depends on the age of the animals at the time of irradiation.

In general, total-body life-shortening irradiation tends to increase the incidence and/or the severity of age-dependent diseases at given chronologic ages [2, 3, 6, 11-14]. One could perhaps assume that total-body irradiation induces each of the diseases of advanced age separately. However, it is more reasonable to regard such uniformity of response as a temporal advancement of the diseases and as evidence that total-body irradiation causes a nonspecific diffuse, subclinical deterioration of the body tissues that advances the onset of many diseases to a roughly equal degree [2]. There are data which suggest that similar effects may occur in man [15].

3. Subclinical Histopathology

In general, the so-called diseases of aging do not develop suddenly to clinical proportions to be recognized as pathologic entities, but are the eventual results of slow insidious subclinical deteriorations in tissues or organs. The various specific terminal diseases which emerge are often only more or less random expressions of more generalized tissue disorders.

Aging animal populations are seen by gross examination and by microscopic examination to deteriorate slowly but generally in progressive fashion before clinically or pathologically recognizable age-dependent disease entities occur. These changes have been observed to occur prematurely following irradiation (11, 12, 16-21).

A fundamental aging change in the adult animal may be defined as a change which occurs consistently and progressively with the passage of time in all temporally aging individuals of the population, in the general phase of life in which the change may be expected, and which is qualitatively independent of variations in clinical history among individuals. Such a change may be detectable initially at different chronologic ages among individuals or may vary quantitatively with disease history or variations in genetic constitution or environment.

The fundamental histopathologic changes of aging seem to be degenerative and atrophic or involutional changes, the end result of which may be described generally as fibroatrophy. This fibroatrophy involves decrease in number of parenchymal cells associated with a decrease in fine vasculature in a process of arteriolocapillary fibrosis and with an increase in density and amount of interstitial connective tissue, constituting an increase in the histohematic barrier (connective tissue barrier between blood and parenchymal cells).

The hypertrophic cellular changes and hyperplastic or metaplastic tissue changes seen with increasing age are generally not among the fundamental aging manifestations and do not occur in all senescent individuals. These changes seem to be either normal physiologic compensatory responses of less affected cells to degenerative changes in related cells or tissues or, like many degenerative changes observed, are secondary to specific disease processes.

It is not yet clear at the histopathologic level which of the three components of the tissue fibroatrophy of "normal aging", i. e., the changes of parenchymal cells, of connective tissue, and of fine vasculature, are primary and secondary with respect to one another; or what are the relative contributions of one component to another, since they have mutual or reciprocal influences; or to what extent these relationships or contributions differ among tissues of different kinds.

Loss of parenchymal cells may be followed by a process of replacement fibrosis and reduction in fine vasculature secondary to reduced parenchymal cellularity. Also, nonspecific damage of the endothelium of fine vasculature may result in interruption or impedence of circulation, increase in interstitial colloid and in fibrillar density of connective tissue, increase in histohematic barrier, consequent loss of parenchymal cells through hypoxia and reduced nutrition, then replacement fibrosis and reduction in fine vasculature. The success of regeneration of parenchymal cells depends greatly on the adequacy of the microcirculation and on the permeability or integrity of the histohematic barrier.

None of these histopathologic components of the tissue fibroatrophy of aging are due necessarily to inherent changes in the tissue components involved. Even the increasing fibrillar density of interstitial connective

tissue may be caused by forces originating elsewhere in the body. All of these changes are nonspecific changes which may be brought about by a variety of agents or factors, including adrenal cortical reactions and perhaps any agent eliciting a response of the adrenal cortex as in stress phenomena. The nonspecificity of basic histopathologic aging changes is compatible with the concept proposed by Jones (18) that aging is a result of the accumulation of nonspecific injuries.

Sublethal, life-shortening total-body irradiation and localized irradiation, by means of external or internal sources of radiation, produces permanent changes in the tissues of experimental mammals preceding the appearance of age-dependent disease entities, which, according to the histopathologic criteria discussed, seem to this author to be essentially identical with the histopathologic manifestations of premature aging (11, 12, 19-21)

This radiation fibroatrophy comprises increase in amount and density of connective tissue, and increase in amount of interstitial mesenchymal elements, constituting an increase in histohematic barrier, reduction of fine vasculature in a process of arteriolocapillary fibrosis, and reduction in number of parenchymal cells.

The following is a description of the author's histopathologic hypothesis of aging and premature aging caused by radiation (Figure 3). At radiation dosage levels causing temporal advancement of age-dependent diseases and life span shortening, the nonspecific damage of endothelium of fine vasculature, by direct or indirect mechanisms, seems to be the change of greatest importance, among the early radiation changes, in the eventual development of the tissue fibroatrophy of "radiologic aging".

HISTOPATHOLOGIC HYPOTHESIS FOR THE

TISSUE FIBROATROPHY OF

AGING AND "RADIOLOGIC AGING"

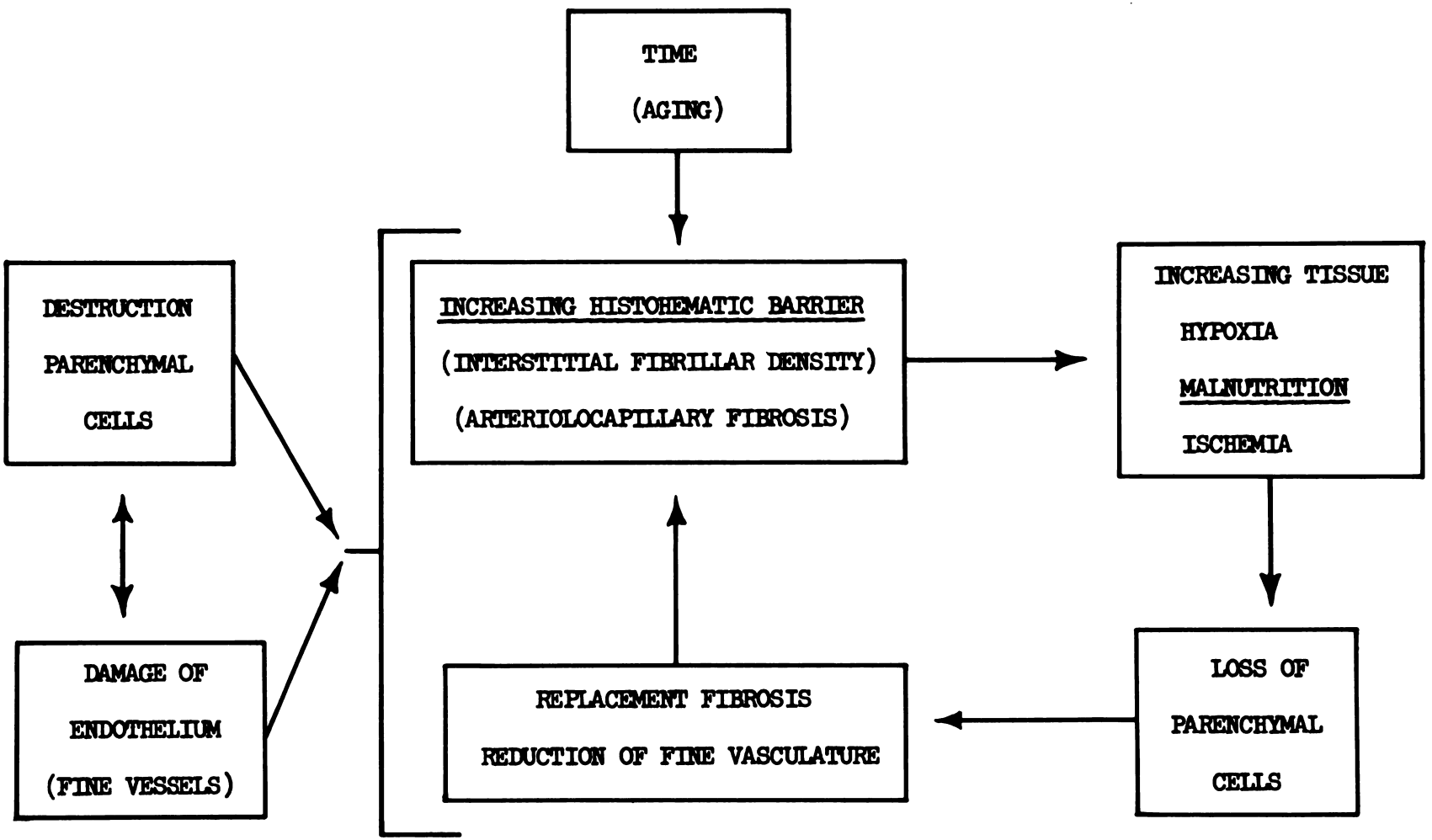

Figure 3. Histopathologic Hypothesis For The Tissue Fibroatrophy of Aging and "Radiologic Aging".

Although some of the damage of the fine vasculature may be due to relatively direct effects of the radiation on endothelial cells, much of it is probably indirect. Some of the indirect damage on fine vasculature in some tissue seems to be due to the initial destructive effect of radiation on parenchymal cells, which varies in degree according to their nature and radiosensitivity from one tissue to another. Secondary to damage of capillary and arteriolar endothelium, there is some degree of pericapillary or interstitial edema and increase in amount of interstitial colloid, followed by an increase in fibrillar density of the interstitial connective tissue. There also develops some increase in subendothelial connective tissue in arterioles. These changes in connective tissues constitute an increase in the histohematic barrier and a temporal advance in the development of arteriolocapillary fibrosis, which are progressive processes in "normal" aging. These manifestations increase progressively with passing time in the irradiated tissues as they do in nonirradiated tissues, but remain temporally advanced in degree in the former as compared with the latter. As these progressive changes gradually reduce the capacity of the vasculoconnective tissues to support the full complement of parenchymal cells, owing to the development of relative hypoxia and malnutrition, the parenchymal cells gradually become decreased in number either as a result of precocious aging and death or as a result also of decrease in cell reproduction in the case of renewable cells. This loss of parenchymal cells occurs earlier in the irradiated tissues than in the nonirradiated tissues, according to the earlier changes in histohematic barrier and fine vasculature. With the gradual decrease in number of parenchymal cells there occurs a "replacement fibrosis" with increase in interstitial mesenchymal elements and further increase in histohematic barrier and with further reduction of fine vasculature secondary

to the loss of parenchyma.

The influence of the early parenchymal damage on the early changes in vasculoconnective tissue and on the late effects or aging manifestations is best described for different types of tissue in terms of the nature and relative radiosensitivity of the parenchymal cells they contain.

Vegetative intermitotic parenchymal cells, which divide regularly but differentiate little or not at all, e. g. basal cells of epidermis, are generally highly sensitive to destructive action of radiation. Differentiating intermitotic cells, which divide regularly and differentiate to some extent between divisions, e. g., myelocytes, are somewhat less sensitive but still relatively sensitive cells in general. Certain mesenchymal elements, including endothelial cells of fine vasculature, are intermediate in sensitivity between these highly sensitive cells and the relatively resistant reverting postmitotic parenchymal cells and the extremely resistant fixed postmitotic parenchymal cells. The reverting postmitotic parenchymal cells are variably differentiated cells which do not divide regularly but are capable of dividing upon appropriate stimulus, e. g. hepatic cells when a partial hepatectomy is performed. The fixed postmitotic parenchymal cells are highly differentiated cells which have lost completely their ability to divide under any circumstances, e. g. the neuron. Some of these, like the neurons, are long-lived, age and die without replacement; others, like polymorphonuclear leukocytes, are relatively short-lived, age and die, but are replaced by the activity of vegetative and differentiating intermitotic precursor cells.

In tissues containing the radiation sensitive vegetative and differentiating intermitotic parenchymal cells, such as epidermis, gastro-

intestinal mucosae, and hematopoietic tissues, the early radiation destruction of these cells depends relatively little on the early radiation damage of vasculoconnective tissue, but the degree of damage of fine vasculature and the change in connective tissue seems to be generally greater in such tissues than in tissues with radiation resistant parenchymal cells receiving similar doses. Following total-body doses in the sublethal life-shortening range, the radiation sensitive parenchyma is regenerated to normal or subnormal levels of cellularity while vasculoconnective tissue changes are "fixed" irreversibly and are progressing with passing time at an advanced level as compared with nonirradiated tissue. Eventually there is a second phase of gradual loss of parenchymal cells secondary to these progressive changes in supporting tissues and premature as compared with nonirradiated tissues. The intermediate period of maintained parenchymal cellularity between the period of regeneration and the beginning of the period of the age involution is shorter the larger the dose, owing to the fact that the vasculoconnective tissue changes are greater the larger or more intense the dose. This intermediate period corresponds with the period of relatively low mortality rate between the period of acute or subacute mortality and the late period of age-dependent mortality.

With the larger doses possible to administer to such tissues under conditions of localized irradiation, there is greater damage of vasculoconnective tissue, greater destruction of parenchyma, directly and sometimes also secondary to marked vascular damage, reduced and delayed regenerative activity of remaining parenchymal cells, due to damage of fine vasculature and connective tissue, and a shorter intermediate period between the regenerative phase and the later involutional phase. In fact, with sufficiently high dose,

there is no intermediate period due to failure of regeneration and the development of early fibroatrophy of the tissue.

In the case of tissues containing the radiation resistant reverting postmitotic parenchymal cells, such as liver and kidney and many other epithelial glands, and tissues containing the irreplaceable radiation resistant fixed postmitotic parenchymal cells, such as muscle and brain and spinal cord, early radiation destruction of considerable numbers of parenchymal cells in direct or indirect fashion requires relatively large doses. Consequently, early destruction of considerable numbers of these parenchymal cells is not seen with total-body irradiation in the sublethal dose range, but only with more intensive localized or generalized irradiation. However, with sublethal irradiation of the whole-body the vasculoconnective tissue changes may be advanced temporally, and the parenchyma, although not appreciably damaged histopathologically in earlier phases, may show precocious loss of parenchyma in the later phase of age-involution secondary to these changes. With increasing doses in localized exposures the temporal advancement of these processes is progressively greater.

Localized aging changes of this kind have been produced in many of the organs of the body by external sources of radiation [3], in radiotherapy patients and experimental animals, and by internally deposited radioactive isotopes [11, 12]. The tissue changes involved in the development of radiation-induced or temporally advanced nephrosclerosis following localized or generalized irradiation from external sources [3, 6] or internal administration of polonium^{210} [11, 12], are histopathologically of the aging type, since the fundamental histopathologic process in aging of the kidney is essentially a nephrosclerotic process.

Internal radioactive substances distributed more or less diffusely throughout the body, such as P^{32}, tend to mimic the picture produced by total-body irradiation from external sources.

Intermediate types of exposure from internal emitters which, although diffusely deposited throughout the body, tend to concentrate differentially among a variety of tissues, may result in different degrees of premature aging change in different parts of the body. For example, polonium^{210} is widely distributed in the body, but tends to concentrate highly in spleen and kidney and certain other organs. Consequently, although the fibroatrophy may be a widespread effect, it tends to be more advanced generally in tissues and organs of highest polonium concentration or radiation exposure, and the causes of death related to nephrosclerosis, hypertension and renal failure are relatively high in incidence (11) at life-shortening dose levels.

4. Physiologic Changes

Associated with the gradual development of the degenerative aging changes generally described as fibroatrophy or involutional change, there seems to be a gradual decline in functional abilities, or more exactly a decline in reserve functional capacities in related tissues and organs. This gradual decrease of reserve capacity may be detectable early provided suitable sensitive tests of the functions are used and provided the functions are stressed. If not stressed but tested under basal conditions, the functional decline may not become apparent until so much of the reserve capacity has been lost that the decline first becomes manifest as symptoms. As the functional reserve of tissue is decreased gradually to a point where ordinary stresses tax function, or function is deficient even under basal

conditions, the tendency to disease from internal conditions and the susceptibility to diseases from environmental factors are gradually increased, as is the probability of death.

A decrease in functional reserve of one vital part by precocious localized aging far in advance of other vital parts tends to increase relatively the probability of disease in the affected part or dependent parts with respect to the natural probability of other common diseases of the species.

Once the degenerative changes and decreasing functional reserve capacities of aging have reached the point at which serious chronic diseases begin to emerge, especially the various chronic progressive disorders of later life, the correlated effects of aging and disease on physiologic processes tend to contribute to the pathogenesis of related disorders, perpetuate themselves by circular reactions, exacerbate other preexisting difficulties, and cause further changes characteristic of aging, further decreasing functional reserves. The pathogenesis of nephrosclerosis and the renal-hypertensive syndrome with consequent generalized arteriosclerosis and its consequences following irradiation is a good example (11).

Unfortunately there has been relatively little study of long-term effects of irradiation on body functions, especially functional reserve capacities, directed toward the problem of aging. However, some of the functional studies which have been done suggest that functions which decline with age tend to decline prematurely as a result of life-shortening irradiation, in accordance with the deterioration of tissue as observed histopathologically.

There is also a paucity of biochemical information on effects of irradiation directly related to manifestations of aging. However, some pertinent data have been obtained which indicate premature aging manifestations following irradiation. One of the most notable examples is the work of Sobel (22) showing premature decrease of hexosamine-collagen ratio following irradiation of skin, indicating a relative decrease of ground substance and a relative increase in collagen. Whether this change is primary or secondary to histopathologic effects of irradiation in vasculature or parenchyma, or represents only the increase in collagenous tissue in replacement fibrosis, is not yet clear.

Conclusion

The foregoing general considerations of actuarial, pathologic, histopathologic, and physiologic changes following irradiation, in comparison with the manifestations of "normal" aging, indicate a strong resemblance between the late effects of life-shortening total-body irradiation and the manifestations of premature aging, especially with respect to the histopathologic manifestations preceding age-dependent disease. The histopathologic changes preceding disease development at the site of localized irradiation from external sources or from internal radioisotopic sources also bear a strong resemblance to the histopathologic manifestations of aging and therefore suggest the concept of premature localized aging resulting from localized irradiation. Although the processes and manifestations of "normal" aging and "radiologic aging" at the histopathologic level are similar, their nonspecificity makes it impossible to predict whether or not the more fundamental underlying processes, whatever they may be, will be similar or quite different.

References

1. A. Comfort. Natural aging and the effects of radiation, Rad. Res., Suppl. 1: 216-234 (1959).
2. H. A. Blair. Data pertaining to shortening of life span by ionizing radiation. USAEC Document UR-442 (1956).
3. Report of the Subcommittee on Long-Term Effects of Ionizing Radiations from External Sources, Committee on Pathologic Effects of Atomic Radiation, NAS-NRC Publication 849, Washington, D. C. (1961).
4. A. M. Brues and G. A. Sacher. Analysis of mammalian radiation injury and lethality, in Symposium on Radiobiology, ed. J. J. Nickson, John Wiley, N. Y. 441-465 (1952).
5. R. H. Mole. Shortening of life by chronic irradiation: the experimental facts. Nature 180: 456-460 (1957).
6. J. Furth, A. C. Upton and A. W. Kimball. Late pathologic effects of atomic detonation and their pathogenesis. Rad. Res., Suppl. 1: 243-264 (1959).
7. G. J. Neary, R. J. Munson and R. H. Mole. Chronic Radiation Hazards, Pergamon Press, London (1957).
8. G. A. Sacher. A comparative analysis of radiation lethality in mammals exposed at constant average intensity for the duration of life. J. Natl. Cancer Inst. 15: 1125-1144 (1955).
9. J. B. Hursh, G. W. Casarett, A. L. Carsten, T. R. Noonan, S. M. Michaelson, J. W. Howland, and H. A. Blair. Observations on recovery and irreversible radiation injury in mammals. 2nd UNIC on Peaceful Uses of Atomic Energy Vol. 22: 178-183 (1958).

10. D. Grahn. The genetic factor in acute and chronic radiation toxicity. 2nd UNIC on Peaceful Uses of Atomic Energy Vol. 22: 394-399 (1958).

11. G. W. Casarett. Histopathology of alpha radiation from internally administered polonium. USAEC Document UR-201 (1952).

12. G. W. Casarett. Acceleration of aging by ionizing radiaton. J. Gerontology 11: 436 (1956).

13. A. C. Upton. Ionizing radiation and the aging process. A review. J. Gerontology 12: 306-313 (1957).

14. P. Alexander. Accelerated aging - a long term effect of exposure to ionizing radiations. Gerontologia 1: 174-193 (1957).

15. Shields Warren. Longevity and causes of death from irradiation in physicians. J. A.M.A. 162: 464-467 (1956).

16. S. Russ and G. M. Scott. Biological effects of gamma irradiation. Brit. J. Radiol. 12: 440-441 (1939).

17. P. S. Henshaw. Experimental roentgen injury. IV. Effects of repeated small doses of x-rays on blood picture, tissue morphology, and life span in mice. J. Natl. Cancer Inst. 4: 513-522 (1944).

18. H. B. Jones. A special consideration of the aging process, disease and life expectancy, in Advances in Biol. and Med. Physics, Academic Press, N. Y. 4: 281-337 (1956).

19. G. W. Casarett. Acceleration of aging by ionizing radiation. USAEC Document UR-492 (1957).

20. G. W. Casarett. Acceleration of aging by ionizing radiations, in The Biology of Aging, ed. B. Strehler, A.I.B.S., Washington, D. C. 147-152 (1960).

21. G. W. Casarett. Interactions between cells and tissues following radiation, in Radiobiology At The Intra-Cellular Level, ed. T. G. Hennessy et al., Pergamon Press, N. Y. 115-135 (1959). Also USAEC Document UR-521 (1958).

22. H. Sobel. Studies on the measurement of aging, in The Biology Of Aging, ed. B. Strehler, A.I.B.S., Washington, D. C. 274-278 (1960).