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Effects of Ionizing Radiations on Aging and Life Shortening in Human Populations

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Introduction

In this presentation some of the findings in irradiated human populations which may be related to aging and life shortening are reviewed. Dr. CASARETT has ably described these changes in animals and Dr. UPTON in his excellent presentation has described radiation carcinogenesis.

Knowledge of late effects of radiation exposure in human beings is scanty and is derived largely from studies of the Japanese people exposed to the atomic bomb irradiation, the Marshallese exposed to fallout, patients exposed to diagnostic and therapeutic irradiation, occupational exposure such as physicians and x-ray technicians, radium dial painters, uranium miners, etc. The development of neoplasia is the most striking late effect of exposure while the development of the less specific changes, many of which are similar to those associated with the aging process, are much less clear-cut.

The role of irradiation in the induction of malignant transformation is well established, and accounts for most of the life-shortening effects observed. The organ or tissue affected is largely dependent on the type of exposure. Penetrating irradiation of large portions of the body are associated with leukemia and, to a lesser extent, with other malignancies as noted in the Japanese exposed to the atomic bomb, medical specialists using irradiation, and patients treated for ankylosing spondylitis. Most malignant tumors, however, have occurred in persons following internal absorption of radioisotopes which are usually selectively absorbed by target organs. Examples are cancer of the bone in the case of radium dial painters, cancer of the lung in uranium miners, liver cancer in patients treated with Thorotrast and thyroid tumors from radioiodine absorption.

Since Dr. UPTON has discussed radiation carcinogenesis, I will confine my remarks to a summary of some of our relatively new data in regard to the development of thyroid neoplasia in Marshall Islanders exposed to radioactive fallout in 1954 and then review certain other late nonneoplastic changes in irradiated human beings which may be related to aging and life shortening.

Thyroid Neoplasia from Radioiodine Absorption in Marshallese Exposed to Fallout

During the 2 days before evacuation of the Marshallese people from their contaminated island, they received a sublethal exposure of γ-irradiation (175 rads), marked contamination of the skin which later resulted in β-burns, and they absorbed significant amounts of radioisotopes from inhalation and ingestion of contaminated food and water[1]. The acute effects of their exposure have been well documented [9, 14]. Though no acute effects of the internally-absorbed fallout were observed, radioisotopes of iodine were absorbed in sufficient quantity to result in late effects on the thyroid. In addition to ^{131}I, several shorter-lived isotopes of iodine ($^{132-, 133-, 135}$I) were absorbed in significant quantity. It was calculated from radiochemical urine analyses that thyroids of adults received about 160 rads from radioiodines and in addition 175 rads from γ-irradiation. Since the children had much smaller thyroids, they received considerably higher doses. It was estimated that a 3–4-year-old child received thyroid doses in the range of 700–1,400 rads from radioiodines and 175 rads from γ-irradiation. The total dose to the thyroid glands compared with other organs of the body was greater by a factor of 2 in adults and about 7 in the children.

Thyroid nodules first appeared in a 12-year-old girl 9 years after exposure (1963), followed by increasing numbers of thyroid nodules in the following years in other exposed people. At present, 19 exposed Rongelap people among 66 now living (of 82 exposed) have developed nodularity and in addition, 2 young boys who showed marked growth retardation developed severe hypothyroidism with atrophy of the thyroid gland [10]. Partial to complete thyroidectomy has been performed on 18 cases. Benign adenomatous nodules were noted in all but in addition, 3 cases had malignant lesions, 1 in a

1 Among the Rongelap people 64 were on Rongelap Island and received the heaviest exposure of 175 rads γ-radiation, 18 others were on nearby islands and received only about 69 rads. A third group of Marshallese were on Utirik Island farther east and received only an estimated dose of 14 rads.

Table I. Thyroid lesions in Marshallese exposed to fallout

Island group (radiation dose-gamma)	Age at exposure	Estimates Thyroid dose rads, radioiodines[1]	Thyroid lesions percent[2]	Malignant lesions percent[2]
Rongelap	<10	500–1400	89.5 (17/19)	5.3 (1/19)
175 rads	>10	160[3]	8.8 (3/34)	5.9 (2/34)
	all	–	39.6 (21/53)	5.7 (3/53)
Rongelap	<10	275–550	0.0 (0/6)	–
69 rads	>10	55	12.5 (1/8)	–
	all	–	7.1 (1/14)	–
Utirik	<10	55–100	0.0 (0/40)	–
14 rads	>10	14	5.1 (3/59)	1.7 (1/59)
	all	–	3.0 (3/99)	1.0 (1/99)
Rongelap	<10	–	0.0 (0/61)	–
unexposed	>10	–	2.3 (3/133)	–
	all	–	1.5 (3/194)	–

1 Dose from $^{131, 132, 133, 135}I$.
2 Based on number now living.
3 Children 10–20 years of age at exposure received doses between 160 and 500 rads.

40-year-old woman (in 1965) and 2 recent cases (in 1969), 1 in a 36-year-old woman and the other in a 21-year-old female[2]. The ages at exposure were 29, 21 and 7 years. The latter case is the first noted in the group of 19 children exposed at less than 10 years of age. Table I summarizes findings in the various populations.

At surgery the thyroid showed multiple discrete nodules a few millimeters to several centimeters in diameter, soft to firm in consistency, and some showed hemorrhagic and cystic changes. Microscopic examination revealed that the benign nodules had marked variation in size of follicles and evidence of radiation damage could be detected in many cells. The malignant lesions were present as one or more firm tumors (see fig. 1) and microscopically varied in structure from papillary to mixed papillary and follicular. All showed capsular invasion. In 2 cases there was localized lymph node metastasis and in 2, localized blood vessel metastasis was seen.

2 One additional thyroid cancer was found in a woman from Utirik Island and in view of the low thyroid dose received by these Islanders (about 30 rads) it is less likely that this case was radiation-induced.

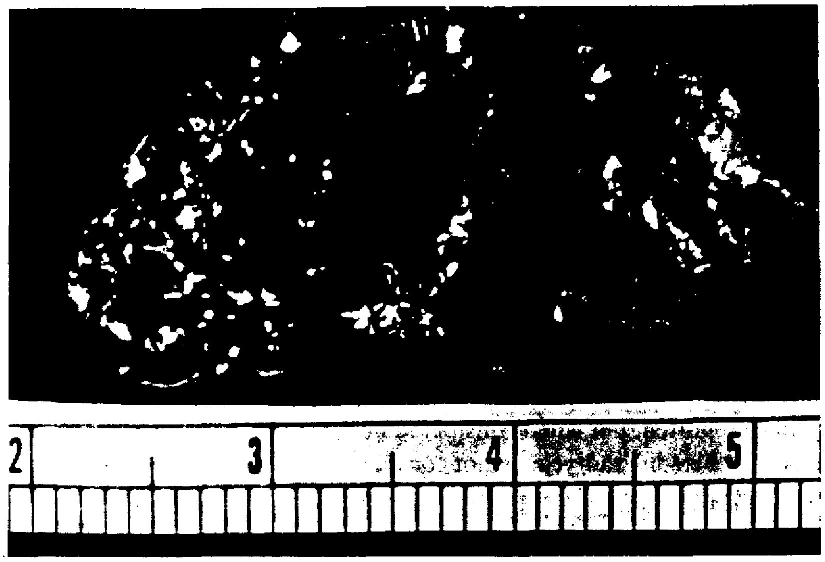

Fig. 1. Malignant lesion in thyroid gland removed from a 41-year-old Marshallese woman who had been exposed to fallout. The malignant lesion can be seen to the right. Localized blood vessel and lymph node metastases were noted.

Slight to moderate growth retardation in some exposed children had been noted beginning several years after exposure to fallout. Though numerous thyroid studies were done, thyroid deficiency was not detected at that time. However, more recently thyroid nodularity along with deficiency in serum thyroxine has been correlated with growth retardation in several children. Supplementary hormone therapy was instituted in the exposed Rongelap people in 1965, the rationale being to prevent the action of the thyroid-stimulating hormone on the injured glands and so hopefully, (a) repress further development of nodules and malignancy, (b) furnish needed hormone in operated cases, and (c) possibly enhance growth in retarded children. It is too early to know if this treatment is helping in the prevention of nodularity but it does appear to have enhanced growth and development in some of the retarded children, particularly in the 2 hypothyroid boys who had shown the greatest retardation of growth.

The importance of late effects of radioiodine exposure is borne out by these findings particularly in the children. Though a few cases of thyroid cancer following radioiodine treatment have been noted, the correlation between treatment and development of the malignancy has usually not been clear-cut.

It appears that the 3 cases of thyroid cancer in the Rongelap people are the first to be clearly associated with radioiodine exposure with the possible exception of a single case reported by SHELINE *et al.* [28].

The incidence of thyroid cancer on a per rad basis in the Rongelap people (5.6 cases/10^6 people/rad/year) is not inconsistent with the incidence reported by others [17] following X-ray exposure of children. It does appear from these findings that radioiodines may be as carcinogenic as X-rays. Perhaps the reason for lack of development of thyroid malignancy in patients treated with radioiodine is related to the high doses of irradiation used which might so damage the glands as to preclude proliferative activity and malignant transformation.

The incidence of benign nodules in the Marshallese is higher than previously reported, but when considered on a risk/rad basis, the incidence of 51 cases/10^6 persons/rad/year is not too different from that reported by PINCUS *et al.* [25].[3]

The data on the Marshallese are too meagre to draw any valid conclusions about dose response relationship associated with radioiodine exposure of the thyroid. Based on his Ann Arbor series and the Marshallese data, HEMPELMANN [17] postulated a linear dose response with no threshold (at least above 20 rads) for radiation-induced thyroid nodularity.

There have been 3 additional cases of cancer (of the female genital tract) in the exposed Marshallese and though no definite malignancy has been reported in the unexposed comparison population, correlation of those malignancies with radiation exposure is uncertain [9].

In spite of a high incidence of 'γ-burns' of the skin in the Marshallese there has been no evidence of late chronic radiation dermatitis or malignant transformation of the burned areas. Some scarring and pigment aberrations are still evident. Since skin cancer usually has a latent period of 20 or some years, it may be too soon to expect such changes in the Marshallese [9].

3 The question was asked this morning concerning the relative radiosensitivity of the thyroid gland of the child compared with the adult gland from radioiodines. From the Marshallese data, we could reason that the increased dose due to the smaller size of the gland was responsible for the higher incidence of nodularity. On the other hand since the infant thyroid grows from about 1–20 g at maturity requiring 4–5 cell divisions, there is a greater opportunity for expression of radiation-induced mutational changes and neoplastic transformation in the developing gland. In the adult gland cell division is seldom observed. Though it is not possible at this time to define a tolerance range for either the adult's or child's thyroid from these data it seems prudent to use caution in the use of radioiodines, particularly in children where the additional possibility of growth and development retardation exists.

Table II. Aging criteria tested. (Combined exposed and unexposed groups)

Criterion	Aging effect	Correlation with age	
		Marshallese	ABCC studies [8]
Lymphocytes, peripheral blood	decrease	0.9	
Lymphocytes transformation[1]	decrease	0.9	
Greying of hair	increase	0.8	0.7
Arcus senilis	increase	0.8	
γ-globulins[2]	increase	0.7	
Skin elasticity	decrease	0.7	0.6
Skin looseness	increase	0.7	
Visual acuteness	decrease	0.7	0.4
Hearing	decrease	0.7	0.6
Hand grip strength	decrease	0.6	0.3
Neuromuscular reaction[3]	decrease	0.6	0.5
Systolic blood pressure	increase	0.5	0.5
Diastolic blood pressure	increase		0.4
Cholesterol	increase	0.4	0.2
Whole body potassium[4]	decrease	0.4	
Heart size	increase		0.3

1 Response of lymphocytes in culture to phytohemagglutinin stimulation.
2 Exposed individuals showed a difference and are not included. See section on immunohematological changes.
3 Light extinction test.
4 γ spectrographic analysis. Represents lean body mass.

Measurement of Aging Changes

I would like now to briefly describe some empirical studies that have been carried out in irradiated populations in an attempt to measure aging and see if there was any correlation with radiation exposure. Though the injurious effect of irradiation in producing aging-like effects no doubt occurs at the time of irradiation, the expression of such injury may not be evident until years later. Since aging changes are poorly understood and therefore, difficult to measure, several investigations by the ABCC [17–19] and in the Marshallese [7, 8, 11] have been conducted to detect aging effects of irradiation by comparison of measurements of recognizable senile changes in age-matched cohorts of exposed and suitable unexposed comparison populations. Many of these changes could be measured directly, others had to be subjectively assessed on a 1–4+ basis. In table II are listed some of these criteria used in decreasing order of their statistical correlation with chronological age. Al-

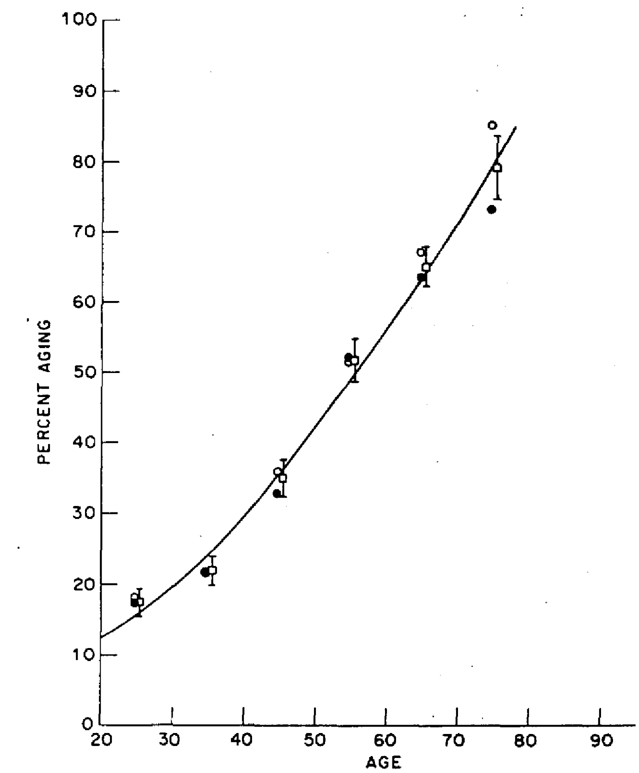

Fig. 2. Combined weighted data (coefficient for age correlation of each criteria used to weight scores before summing). ○ Exposed, ● unexposed, □ combined with standard error means. $r = 0.99$ (correlation with age significant at 1% level), $y = 0.51 + 0.38x + 0.01x^2$.

though many of these criteria showed good correlation with age, no radiation-induced aging effects were detectable since there were no significant differences in the exposed compared with the unexposed groups in these studies. By combining data on a percentage response basis it was possible to obtain a 'biological age score'. The lack of correlation with radiation exposure with such scoring in the Marshallese is demonstrated in figure 2. Perhaps these tests were not refined enough to detect aging effects of irradiation since such changes may be too subtle to be detected in this manner. In any event, most of these criteria are probably not associated directly with lethality.

It is believed these cross-sectional studies will be improved with further testing of these populations on a longitudinal basis. The addition of more tests involving organ function would also be desirable. Until we understand more about the chain of events leading to radiation-induced aging, we will probably continue such studies using the empirical approach. Hopefully, they may lead to clues which will suggest more fundamental studies.

Some Nonneoplastic Late Findings Related to Radiation Exposure

Life shortening. As has been pointed out, the role of irradiation in bringing about life shortening from the development of malignant lesions, particularly leukemia, is well established in animals and man. However, life shortening from other late effects is better established in animals than in man. Studies of mortality in medical specialists using ionizing radiations, particularly radiologists, from about 1930 to 1954 have been reported by several investigators [5,13,27,31,32]. During the early years when radiation protective measures were not as good, radiologists received larger amounts of radiations than other physicians. Studies of mortality tables in the various medical specialties showed that radiologists had a shortening of lifespan of about 5 years. Most of this reduced lifespan was due to leukemia and to a lesser extent to other malignant tumors, but life shortening was still detectable from other causes where these malignancies were subtracted. COURT-BROWN and DOLL [13] in studies not strictly comparable, did not show any difference in longevity in British radiologists. Recently BEBEE *et al.* [2] reported on 13,000 deaths occurring between 1950 and 1966 among 82,000 Japanese victims of atomic bomb exposure. They reported '...once cancer is removed from the list of natural causes, mortality appears to bear no relation to radiation dosage. In none of the four time periods is there evidence of general increase in mortality that one might expect from the hypothesis of accelerated aging.' In regard to the Marshallese population the numbers exposed are too small to give reliable assessment of life shortening effects.

Lens opacities. Opacities of the crystalline lens of the eyes have been noted as a late effect of irradiation in cyclotron workers [1], patients receiving irradiation to the eyes [23] and in the ABCC studies [6,29]. Such lens changes range from posterior subcapsular plaques and flecks visible only with slit lamp examination to frank cataracts in a few cases with reduced vision. In recent studies on the Marshallese people, BATEMAN found an evidence of in-

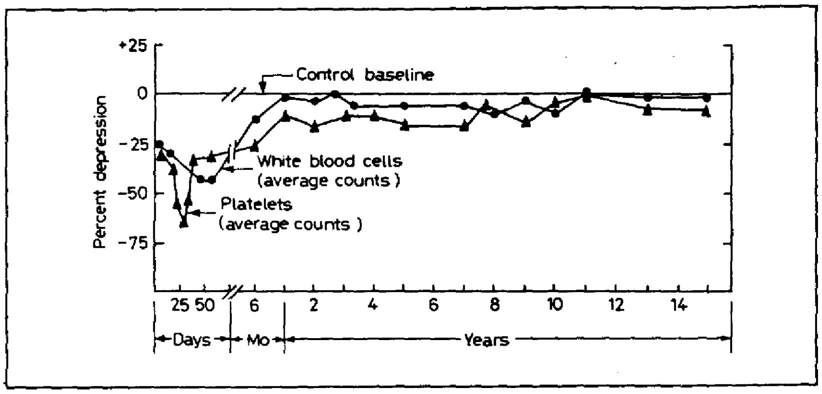

Fig. 3

crease in flecks in the lens of females exposed during adolescence [9]. These data also suggested that variation of sex hormones might play a role in radiosensitivity of the lens.

Chromosome aberrations. Evidence for persisting damage to the genetic apparatus of the cell in the form of chromosome aberrations in lymphocytes of peripheral blood cultures has been noted in several irradiated populations (laboratory accident cases [3], Marshallese [22], Japanese fishermen [21] and the Japanese exposed at Hiroshima and Nagasaki [4]). The incidence was low but the aberrations were noted as late as 20 years after exposure in the Japanese. Such chromosome changes have also been noted in cultured thyroid cells years after radiation therapy [15], and are no doubt present in other cells of an irradiated individual. Such findings lend support to the somatic mutational theory of aging.

Immunohematological changes. There are certain findings in exposed Rongelap people indicating reduced immunological potential. Based on peripheral blood counts, recovery from the acute depression of white blood cells and platelets which was noted during the first 6 weeks after exposure was nearly complete by 1 year but continued to fluctuate at a level slightly below the unexposed populations in subsequent years (see fig. 3). However, it is not certain that such peripheral blood counts reflect bone marrow injury. During the past few years we have carried out certain immunohematological tests on the Marshallese and found that the exposed people have increased albumin levels and significant reduction in γ-globulin levels (about 17 % below

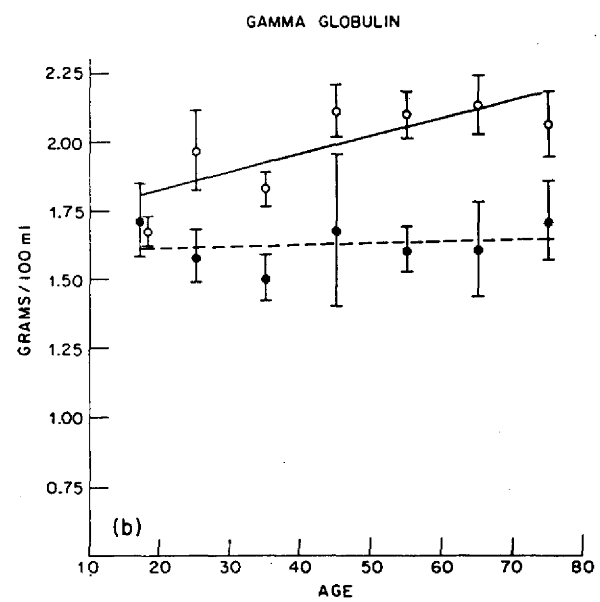

Fig. 4. Age related change in γ-globulins showing the mean level for each decade with standard deviation. ○——○Unexposed, $y = 1.69 + 0.006\ x$. ○——○ Exposed, $y = 1.60 + 0.001\ x$.

those of unexposed levels) with reduced immunoglobulin levels particularly IgG and IgA [11,12] (see fig. 4). The response of cultured lymphocytes from peripheral blood to phytohemagglutinin stimulation, however, was about the same in the exposed as compared with the unexposed population. Though these findings may indicate impairment of immunological capacity in exposed people, such impairment has not been evident based on incidence and severity of diseases compared with the unexposed groups over the 16 years of examinations [9].

Growth and development. Though large doses of irradiation to the bones are known to retard growth in children, it is questionable if such bone exposures in the sublethal dose range can bring about retardation of growth. Some degree of retardation in growth and development in the Japanese children, particularly in males, has been reported by RENOLDS [26], NEHEMIAS [24] and GREULICH *et al.* [16]. The latter authors emphasize the importance of complicating factors such as trauma, nutritional deficiencies, etc. in this population. We have found definite growth retardation in some of the Marshallese children exposed to fallout [30]. As was pointed out earlier, thyroid injury from radioiodine exposure appears to have been responsible for this retarded growth [10].

Nephrosclerotic changes. Such changes have been noted only in patients receiving large doses to the kidney, but have not been reported in persons receiving sublethal doses of whole body irradiation.

Summarizing Remarks

Malignant transformation is usually viewed as a process of aging since the incidence increases with aging. The development of such malignancies is one of the best correlated late effects of exposure in both animals and human beings and is responsible largely for the life shortening observed. Such malignancies have been noted following whole body, partial body or specific organ exposure due to selective absorption of radioactive isotopes. Following whole body (sublethal) exposures, leukemia is definitely established as a late effect and it appears that thyroid cancer as noted in the exposed Japanese can be added to the list. Since malignancies other than leukemia were increased in radiologists (a study covering a relatively long period of time) other types of radiation-induced malignancies may yet appear in the exposed Japanese and Marshallese populations.

Heretofore radioiodines had not been thought to play an important role in malignant transformation. However, the recent development of the high incidence of both benign and malignant nodules in the Marshallese described in this paper clearly indicates the importance of radioiodine exposure in this regard. The high incidence of thyroid abnormalities in the Marshallese children along with the related retardation of growth emphasizes the caution that must be observed in the use of radioiodines.

Many of the nonspecific effects of irradiation bear similarities to ordinary aging changes. Since the underlying changes of ordinary aging are not clearly defined, it is understandable that such radiation-induced changes are even less understood. There are no pathognomonic radiation changes characterizing late effects. Measurement of the usually-recognized aging changes in the exposed Japanese and Marshallese populations have failed to reveal such effects of irradiation. However, late effects other than neoplasia have been found in irradiated human populations such as life shortening in radiologists, development of lens opacities, persistence of chromosome aberrations and certain immunohematological changes. Most of these effects such as cataracts, skin changes, chromosome aberrations, etc. do not appear to be related to lethality, though collagenous and fibrotic changes in connective tissue and blood vessels may indirectly have a causal relationship to mortality. The individual genetic predisposition to such alterations is an important area about which we know little. Also complicating environmental factors (socio-economic, geographical, stress of trauma, heat, cold, disease epidemics, etc.) no doubt play an important role in the development of late radiation effects.

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