Rongelap

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AGEING STUDIES IN A MARSHALLESE POPULATION EXPOSED TO RADIOACTIVE FALL-OUT IN 1954

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The Marshallese people who had been accidentally exposed to radioactive fall-out in 1954 have been examined annually since the accident for possible late effects of radiation, including the development of premature ageing. The accidental exposure of these people occurred on March 1, 1954 as a result of an unpredicted shift in winds following experimental detonation of a large thermonuclear device at Bikini in the Marshall Islands. A white, snow-like, highly radioactive material was deposited on the island and its 82 inhabitants. There were 64 people (55 now living) who received about 175 rads of whole-body gamma radiation, exposure of the skin from fall-out deposited thereon, and also significant internal absorption of radionuclides. Eighteen other Rongelapese (14 now living) were on a fishing expedition on a nearby island and received less than half the exposure of the other group. Evacuation of the islanders was accomplished two days after the accident. They were returned three years later (1957) when radiation levels on the island were considered safe. Since the accident over 200 Rongelap people or their relatives who had not been exposed to fall-out returned to live with the exposed people and have formed the comparison population.

Acute effects from exposure were noted in the Rongelap people during the first few months and consisted largely of early transient gastrointestinal and skin symptoms, followed by depression of lymphocytes, neutrophils, and platelets to one-half to one-third normal levels. The hematopoietic depression however did not result in any obvious infections or significant bleeding. "Beta burns" of the skin along with spotty epilation of the head were wide-spread during the first several months after exposure. No acute effects from the internal absorption of radionuclides were noted. No fatalities occurred, and the people had largely recovered from these acute effects of exposure by the end of the first year.

Subsequent examinations have largely been concerned with the possible late effects of radiation. The most significant such finding has been the development of thyroid nodules and hypothyroidism during the past three years among the exposed people. This development is believed to be a late effect of radiation of the thyroid gland from internal absorption of radioiodines and from external gamma radiation at the time of the fall-out. During the two day period following the accident, before the evacuation of the people occurred, the inhabitants absorbed radionuclides in the fall-out by inhalation and ingestion of contaminated food and drinking water. Based on radiochemical analyses of pooled urine samples taken several weeks after the accident, it was estimated that the adult thyroid gland received about 160 rads from the radioiodines, in addition to 175 rads from the external gamma radiation. In view of the smaller thyroid glands of the younger children, it was estimated that they received in the range of 700-1400 rads in the more heavily exposed group. As of March, 1966, a total of 16 cases of nodules of the thyroid gland and two cases of hypothyroidism had been detected. The largest incidence(79%) has occurred in the children exposed at less than 10 years of age. No such pathological change has been noted in unexposed children or children in the lesser exposed groups. Thyroid surgery has been performed on 11 cases with nodules. Ten of these cases, 9 children and one adult, were all found to have benign nodules. One 41 year old woman was found to have a cancer of the thyroid. Description of these thyroid lesions as well as the possible radiation etiology has been discussed in a recent paper (Conard, Rall and Sutow 1966). A general review of the findings in the Marshallese can be found in other references (Cronkite, Bond, Conard, Shulman, Farr, Cohn, Dunham and Browning 1955, Conard and Hicking 1965).

There are few other so-called late effects of radiation which can, with reasonable certainty, be ascribed to exposure in these people. Among these was an increased incidence of miscarriages and stillbirths noted among the exposed women during the first four years after exposure; lag in complete recovery of peripheral white blood cells and platelets to levels of the non-exposed comparison population; and slight retardation of growth and development of children, particularly boys exposed at less than five years of age. A hypothyroid etiology for growth retardation is strongly suggested by the recent findings of definite hypothyroidism in two of the most retarded boys in the Group (Conard et al. 1966; Sutow, Conard and Griffith 1965). General health and fertility have been about the same in the exposed as in the comparison population. The mortality rate has been somewhat higher in the exposed population but this population has a larger percentage of older people. Possible life-shortening effects of radiation can be best evaluated in the future.

This report concerns an attempt to evaluate possible effects of radiation on the ageing process in the exposed population. During physical examinations ageing effects are usually referred to in a general qualitative sense. In order better to evaluate possible ageing effects, a more quantitative approach was indicated. There are a large number of criteria which have at one time or another been regarded as being age dependent. These studies represent an effort to select criteria which could be carried out under conditions of these examinations. The overall objective has been to combine the scores of the various criteria into one "average age score" for each individual, comparing scores in the exposed with the unexposed comparable age groups. An earlier attempt to quantify these ageing criteria were presented in a previous publication (Conard 1960). In this report several new criteria have been added with further statistical treatment of the data.

Materials and methods

The study was hampered by the small number of people involved, lack of vital statistics on the Marshallese people, the language barrier, as well as uncertainty of exact ages in some of the older people.

The ageing criteria to be presented were recorded only in adults (20 years of age and older). Data were recorded on 90 adults, 36 adults in the originally exposed group and 55 in the larger comparison population. The ages were reasonably well distributed except for a small number of people greater than 60 years of age.

In selecting the criteria to be used the above mentioned difficulties limited the extent and usefulness of those tests which require motivation and co-operation on the part of the subject. Several tests were tried and discarded for these reasons, including vital capacity and cardiovascular response to two-step test. Also not included were several tests that were difficult to quantify such as baldness, retinal and peripheral arteriosclerosis. Several other tests were eliminated due to poor correlation with ageing such as serum folic acid and Vitamin B_{12} levels.

In this report 14 criteria of ageing are presented: four involve the special sense organs (visual acuity, accommodation, arcus senilis, and hearing loss); three involve neurological or neuromuscular function (vibratory sense, reaction time, and rapidity of movement); three involve the integument (skin looseness, skin elasticity, and hair greying); one test of strength; one cardiovascular test (systolic blood pressure); and two miscellaneous tests (serum cholesterol and body potassium). Two of the tests required subjective evaluation on the part of the examiner (hair greyness and arcus senilis); 7 required varying degrees of motivation and co-operation on the part of the subject (visual acuity, accommodation, hearing loss, vibratory sense, reaction time, neuromuscular function, and strength); 5 tests involved direct measurements (skin looseness, skin elasticity, systolic blood pressure, body potassium, and serum cholesterol).

Integument. A special caliper with constant spring tension was devised for skin examinations and the caliper and methods of skin examination have been previously described (Conard 1960; Hollingsworth, Goro and

Conard 1961). (1) Skin looseness: The skin fold at the junction of the chin and neck was measured in millimeters as described previously. (2) Skin elasticity: Measured on the back of the hand by allowing the caliper to pinch a fold of skin for one minute and measuring the time for the skin fold to retract to the surrounding skin surface. The exact endpoint was sometimes difficult to measure in older people, and if the fold had not retracted completely in 90 seconds, this time measurement was used as maximum. (3) Greying of the hair: The degree of greying of the hair was expressed on a zero to four plus scale as follows: 0, no greying; 1+ slight "salt and pepper" greying; 2+ moderate "salt and pepper" greying; 3+ nearly complete greying; 4+ complete greying.

Special Senses. (1) Eyes: (a) Accommodation. Accommodation was measured in diopters by use of the Prince refracting rule. The average reading of the two eyes was used. (b) Visual Acuity. Visual acuity was measured by Snellen's test. It was found that by taking the square root of the average visual acuity (denominator) of the two eyes the scale was more compressed and more linear. Thus the best vision of 20/10 was represented at 3.2 (the square root of 10), the worst reading of the 20/200 was represented as 14.1 (the square root of 200), and intermediate readings similarly recorded. (c) Arcus Senilis. Estimated in the 0-4+ scale. Only slight limbic clouding was considered 1+ with increasing clouding to marked clouding as 4+.

(2) Ears: (a) Hearing. Audiometric examinations were carried out in a special cubicle lined with acoustic tile. A rugged screening type audiometer was used. Impairment of hearing was averaged for the two ears as follows: the decibel loss for each of the six frequencies (200, 500, 1000, 2000, 4000, 7000) for each ear was averaged and a mean frequency loss in decibels for the two ears was obtained.

With regard to the reliability of determinations using the Prince refracting rule, Snellen's test and hearing acuity, it should be pointed out that these tests were carried out under standardized conditions, but in view of the necessity of using an interpreter under field conditions, it was not feasible to repeat the test by more than one examiner. It is believed, however, that the data from these tests were sufficiently reproducible to be of relative value, although not so accurate perhaps as might be obtained under more desirable conditions.

Cardiovascular Changes. (1) Systolic Blood Pressure. Obtained with the standard aeronoid cuff type sphygmomanometer. Two readings were obtained and the average of the two was used. There was no basic or adjusted level of physical activity such as resting for a standard period of time prior to the readings. Pressures were taken from the left arm with the subject supine during the course of the physical examination.

Neurological and Neuromuscular Function. (1) Vibratory Sense. Vibratory perception was measured over the head of the left tibia by an electric vibrometer, the instrument set at a standard frequency of 120/sec at 20 volts. The endpoint was the voltage intensity required for perception of the vibration. (2) Neuromuscular Function. Measured by having the subject depress the key of a hand talley type of blood cell counter as many times as possible in the period of one minute. The total number of depressions represented the score. (3) Light Extinction Time. A battery of lights were connected in random series and the subject extinguished each light as it appeared. The total time necessary to extinguish all of the lights was measured. This test involved both manual dexterity and mental reaction time (Hollingsworth, Hashizume and Jablon 1965). (4) Hand Strength. Measured by a Smedly hand dynamometer (S. H. Stoelting Co., Chicago, Illinois.) The spring tension of the hand grip was measured in kilograms. The maximum squeeze strength in the dominant hand in three tries was recorded.

Miscellaneous Tests. (1) Body Potassium Levels (^{40}K). Since loss of muscle mass occurs with ageing and total-body potassium is closely related to muscle mass, it has been shown that body levels of potassium decrease with age (Anderson and Langham 1959; Allen, Anderson and Langham 1960). Whole-body spectrographic analyses were carried out in the Marshallese using a lead-shielded structure. In this way ^{40}K levels were obtained and presented as K/kg body weight. Accuracy of these data could have been improved by obtaining more precise determinations of lean body mass, such as by measurement of body water (Allen, Anderson and Langham 1960). (2) Blood Serum Cholesterol Levels. These were obtained on sera which had been returned from the Islands.

In order to place all of the data from each criteria on a common basis for comparison and combination, the data were converted to a percentage basis for each criteria. In the case of the measured data, values associated with least ageing were chosen as zero percent (sometimes the highest reading, as with hand strength; sometimes the lowest, as with hearing loss), and conversely the values showing most ageing were chosen as 100%. The estimated criteria with values of 0, 1+, 2+, 3+ and 4+ were presented as 0, 25, 50, 75 and 100% respectively. The data were examined on an individual basis as well as on a population basis, comparisons were made largely by using means for each decade age group.

An analysis of variance was used to determine differences among the factors of sex, age, and radiation levels. These data were programmed and analysed on a high speed digital computer (The Control Data Corporation 6600 at Brookhaven National Laboratory). For each criterion, the combined score over sex and radiation level was correlated with age. A curve of second degree in age was used when there was a significant departure from linearity. The criteria vibratory sense, hand grip, light extinction time, hand tally count, and body potassium showed significant sex differences, and therefore were scaled for each sex (zero to 100%).

An attempt to correlate a combined "physiological" age score with chronological age was done by obtaining a weighted average score for combined criteria for each age group (see Table I). The absolute value of the correlation coefficients were used as the weighting factor. This has intuitive appeal, since the influence on the final combined score of any particular ageing criterion is proportional to the absolute value of its correlation with age.

Results

The results of these tests are presented graphically in figs. 1-14 and in Table I. The mean values for each decade starting at age 20 are plotted at the midpoint of that decade for exposed and unexposed groups separately and combined, along with the standard errors of the means. The curve or straight line (whichever best represents the particular data) is drawn and its equation presented. The coefficient of correlation with age and significance is also presented. Most of the criteria show good correlation with ageing. It is apparent that most of the criteria show the least change with age in the younger age groups, from 20-40 years of age, particularly for systolic blood pressure, hearing, visual acuity, neuromuscular functions, and skin retraction. Above about 40 years of age the criteria show the greatest change. With a few criteria, changes in the older age group tend to level off or be less steep (accommodation, visual acuity, skin looseness, cholesterol).

In Table I age and radiation dependence of these criteria are presented. The criteria are arranged in descending order of correlation with ageing as shown by the correlation coefficients. In those criteria in which sex differences were apparent, the r value for the two sexes were averaged to determine the overall correlation with ageing. Though there were isolated significant differences between the exposed and unexposed age groups for some criteria, no meaningful pattern emerged. The table shows that the correlation with radiation effects, comparing exposed and unexposed groups, is not significant at the 5% level for any of the criteria. The overall 7% increase in ageing effects in the exposed group is not significant ($p = 0.27$). In fig. 15 the composite weighted biological or physiological age scores are graphically plotted against chronological age (means per decade). Combined mean values for exposed and unexposed groups are also presented with standard errors of the means. The overall correlation of the biological age scores with chronological age is very good (see Table I). The biological

TABLE I

Correlation of criteria with age and radiation exposure

	Correlation With Age; r Value	Correlation With Radiation	
		Percent	Significance *(P)
Greyness	0.87	+17.0	N.S. (0.70)
Arcus Senilis	0.83	0.0	N.S. (1.00)
Accommodation	0.81	-14.1	N.S. (0.11)
Skin Retraction	0.74	+ 7.3	N.S. (0.68)
Skin Looseness	0.70	+ 1.6	N.S. (0.82)
Vibratory Sense (M+F)	0.70**	- 1.4(M), +24.6(F)	N.S. (0.90, 0.20)
Visual Acuity	0.69	+14.0	N.S. (0.59)
Hearing Loss	0.67	+ 7.9	N.S. (0.40)
Hand Grip (M+F)	0.67**	+13.8(M), +13.8(F)	N.S. (0.15, 0.18)
Reaction Time (M+F) (light extinction test)	0.64**	- 2.0(M), -10.5(F)	N.S. (0.88, 0.55)
Systolic Blood Pressure	0.55	-11.5	N.S. (0.30)
Potassium (M+F)	0.41**	-14.6(M), +10.6(F)	N.S. (0.17, 0.22)
Cholesterol	0.39	-17.2	N.S. (0.0501)
Neuromuscular Function (M+F) (hand talley)	0.36**	+ 3.2(M), + 1.1(F)	N.S. (0.85, 0.95)
Combined Score***	0.99	+ 7.0	N.S. (0.27)

* N.S. - not significant at 5% level.
** r values for males and females averaged.
*** Weighted according to r value

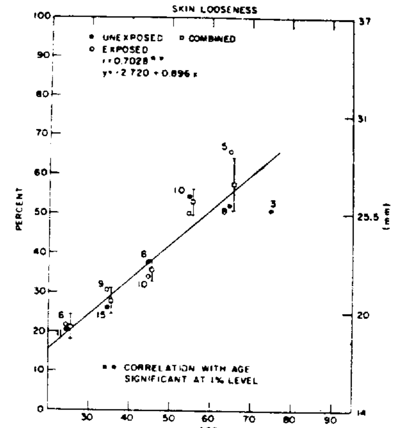


FIGURE 1

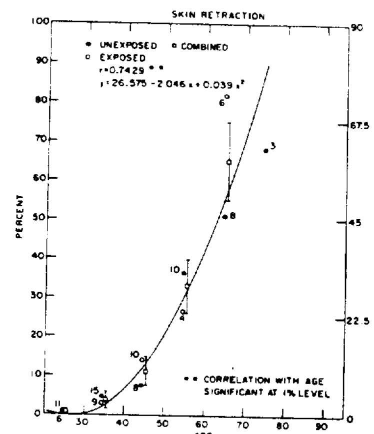


FIGURE 2

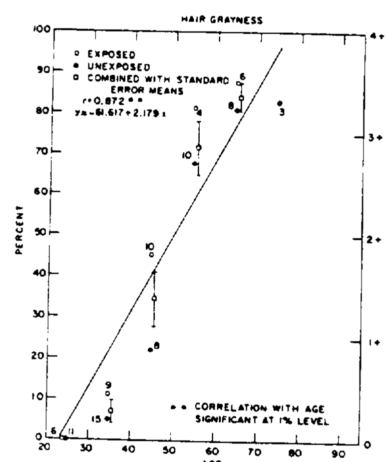


FIGURE 3

Figs. 1-3. Age related changes in skin and hair.

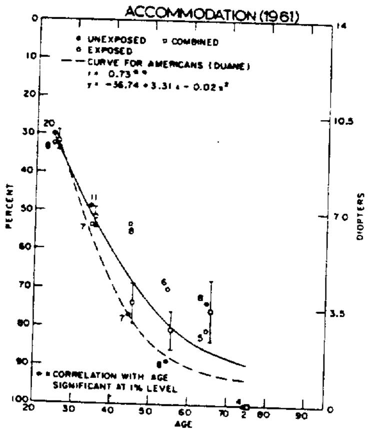


FIGURE 4

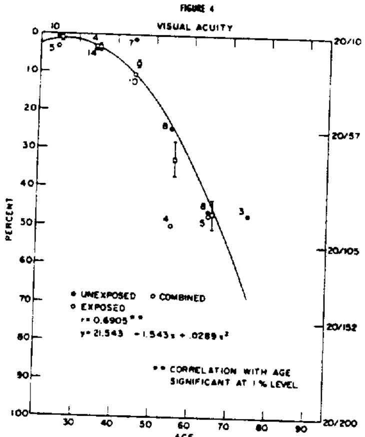


FIGURE 5

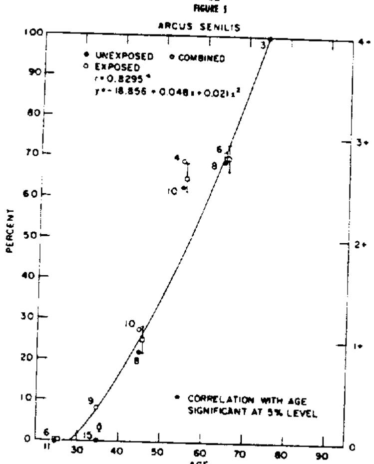
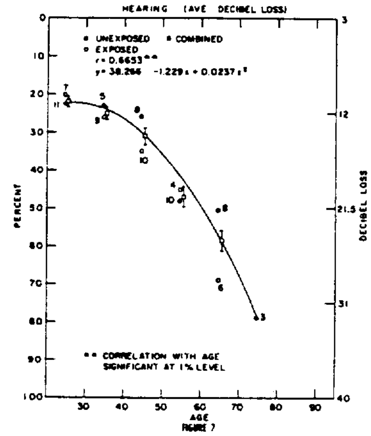
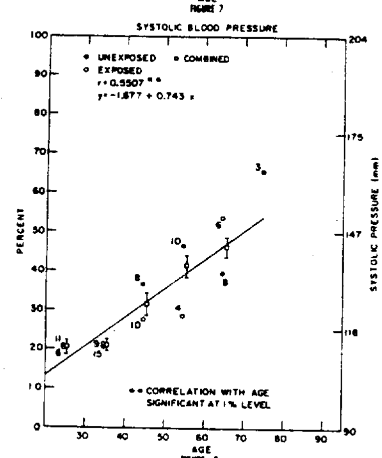
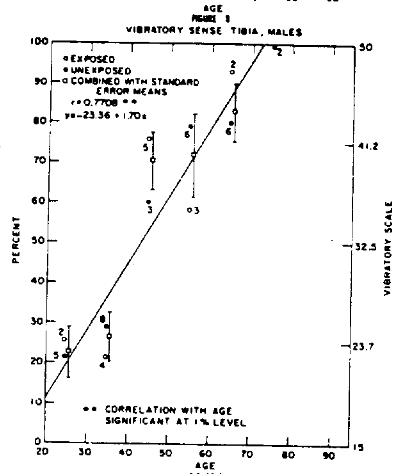


FIGURE 6

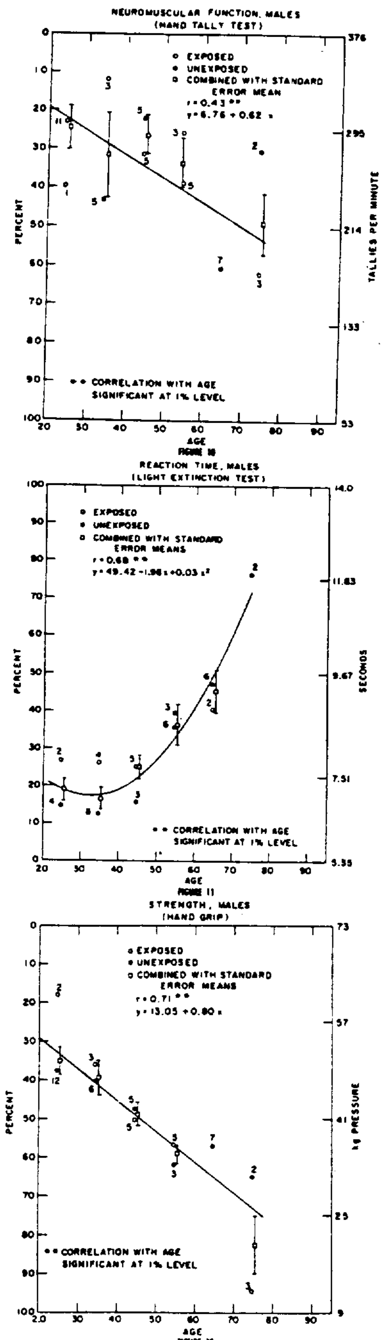
. Age related changes in accommodation, visual acuity, and and incidence of arcus senilis.







Figs. 7-9. Age related hearing loss (fig. 7), increase in systolic blood pressure (fig. 8), and vibratory sense (fig. 9).



Figs. 10-12. Age related decrease in hand tally scores (fig. 10), Age related change in reaction time (fig. 11), Age related loss of hand grip pressure (fig. 12).

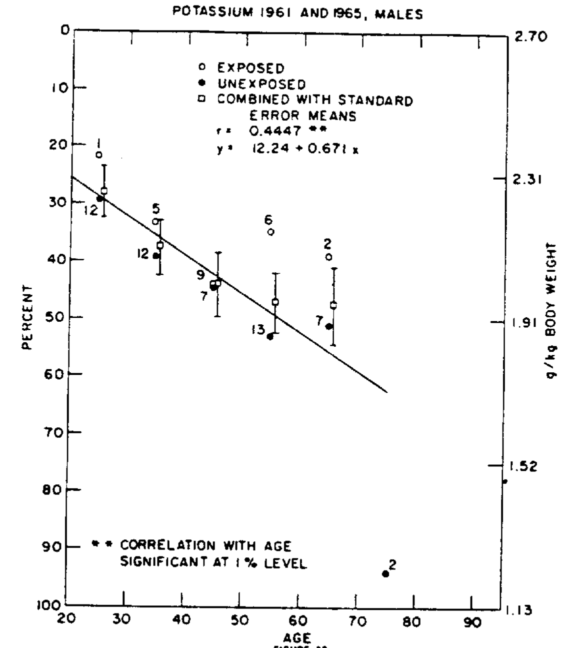


FIGURE 13

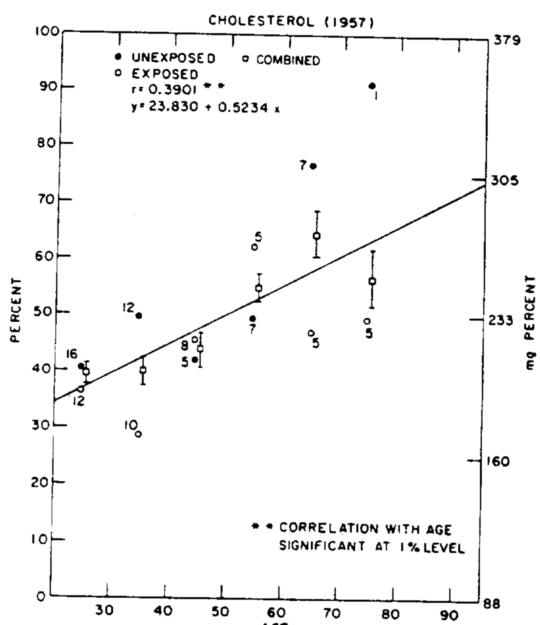


FIGURE 14

Figs. 13 and 14. Age related changes in blood chemistry. Potassium (fig. 13), cholesterol (fig. 14).

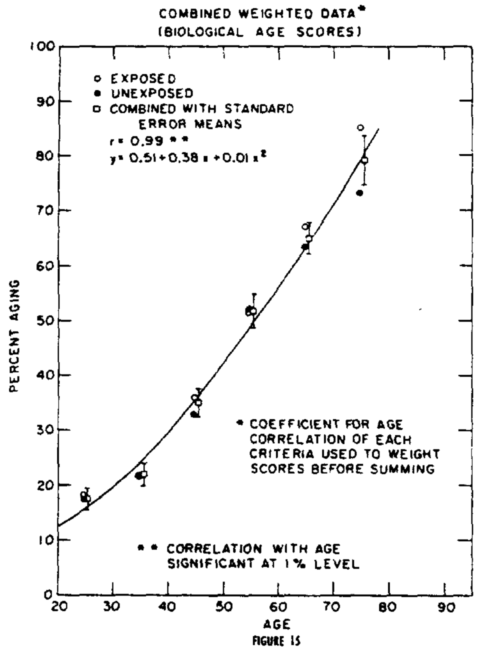


Fig. 15. Biological age scores in exposed and unexposed groups.

"age curve" (Fig. 15) shows that there is less change in the younger age groups than occur after about age 40. Mean values for exposed and unexposed are not significantly different.

Discussion

Though the criteria presented in this report show changes which are definitely correlated with chronological age on a group basis, such correlation is much less accurate on an individual basis. These tests of ageing are least useful in the younger age groups (20-40 years of age), since most of the criteria either are not present until later or if present show slight increase during this age period. Therefore, more sensitive tests are needed to show ageing in these groups.

Effects of radiation on ageing as measured by these parameters were not detected in this population. Perhaps the tests were not sensitive enough to detect such effects at the level of radiation exposure sustained. It is not known if any of the "ageing parameters" which are ordinarily associated with senescence are necessarily associated with radiation ageing, since the latter is very poorly defined or understood. Even if they were, it does not necessarily mean that they are related to mortality which is a more pertinent correlation. Such criteria as hair greying, arcus senilis, neuromuscular function, etc., would not seem to have any obvious relation to mortality. On the other hand, loss of vigor and organ disfunction could well predispose to the development of old age diseases which would enhance mortality. Increase in mortality and life-shortening in the exposed Marshallese is difficult to assay in view of the small numbers of people involved and the slightly greater number of older people in the exposed group compared with the unexposed group.

One radiation effect which might be classified as ageing is the induction of malignant disease at an earlier time than it would ordinarily be manifest. One aspect of this phenomenon may be related to rapidity of cell proliferation (generation cycle) in a particular tissue, i.e. with more rapidly proliferating cells of the bone marrow, leukaemia occurs relatively soon after irradiation, while malignant lesions of the skin would not become manifest until later in this more slowly proliferating tissue. In the Marshallese, the high incidence of adenomatoid goitre in the more rapidly proliferating thyroid glands of the children may possibly represent premature appearance of lesions which are known to occur later in life and thus in a sense represent an ageing process. On the other hand, the fact that no tumours (except benign nevi) have been noted in the heavily irradiated skin of these people might indicate a longer induction period was necessary due to slower cell turnover of the skin.

In considering future ageing studies in the Marshallese it is hoped that more sensitive tests of vigour and organ function suitable to the conditions of study may be used. However, it must be borne in mind that such subtle ageing effects may not become detectable by ordinary clinical means until the organ or tissue shows advanced morbidity. It is hoped that longitudinal studies of ageing criteria in Rongelap individuals and groups may be more rewarding as time goes by.

Acknowledgments

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Summary

Late effects of radiation in a Marshall Island population accidentally exposed to radioactive fall-out in 1954 are reviewed. The most significant findings have been in regard to the development of thyroid abnormalities which have occurred largely in children exposed at less than 10 years of age, and presumably caused by irradiation of the thyroid gland from internal absorption of radioiodines in the fall-out and gamma radiation. Possible radiation induced ageing effects were studied in 90 adults, 36 exposed and 55 unexposed by measurement of 14 criteria usually associated with ageing

(skin elasticity and looseness, hair greyness; accommodation, visual acuity, and arcus senilis of the eyes; hearing loss; nervous and neuromuscular function and vibration sense, light extinction test, rapid movement test, and hand grip strength; systolic blood pressure, blood cholesterol level, and body potassium (^{40}K)). Analysis of variance was used to determine correlation with age and the data for each criterion were weighted according to this correlation factor. Combined scores for all criteria gave a measure of "physiological" age as compared with chronological age on an individual and group basis. Most of the criteria showed good correlation with age on a group basis, less so on an individual basis. Between 20 and 40 years of age the criteria showed less change than after that age. No significant differences were noted between the exposed and unexposed groups. It was postulated that if there were ageing effects from the dose of radiation received by this population more sensitive tests would be necessary to show them. Longitudinal studies of individuals and groups in this Marshallese population might be more rewarding in the future.