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THYROID NODULES AS A LATE EFFECT OF EXPOSURE TO FALLOUT*

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During the past 5 years thyroid abnormalities have developed in a Marshallese population who were accidentally exposed to radioactive fallout in 1954. The accident occurred when a thermonuclear device was detonated at Bikini in the Pacific Proving Grounds. The yield was larger than expected and since the fireball touched the ground, a large amount of incinerated coral and debris was mixed with the radioactive cloud. An unexpected shift in winds occurred high aloft and instead of the cloud going in a northerly direction over the open sea, it veered to the east dropping radioactive fallout on several inhabited islands. The fallout exposure of the Marshallese people was different in many respects from the exposure of the people of Hiroshima and Nagasaki to the effects of the atom bomb detonated over Japan. In Japan the injuries were produced by direct irradiation from gamma rays and neutrons, and from physical injuries from blasts and burns. Psychic trauma, malnourishment, and disease complicated their radiation injuries. Little or no fallout was involved. In contrast the radiation exposure of the Marshallese people

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was all due to the fallout with no physical trauma or thermal burns and little or no psychic trauma.

Table I shows the island groups involved. The 64 Marshallese on Rongelap atoll received the heaviest exposure and it is this group that has shown the major radiation effects. Effects in this group along with the 18 Rongelap people who were on Ailingnae island at the time will be presented here.

Figure 1 shows a rough map of the fallout pattern involving these islands. All of the island groups were evacuated about 2 days after the accident and taken to a naval base to the south where extensive medical examinations and personnel decontamination were carried out over a 3 month period. At the end of this time the American service men had shown few effects of their exposure to radiation and were returned to their stations. The Utirik people had shown little or no effect of their exposure and were returned to their island. However, Rongelap island was too contaminated and the people lived in a temporary village in a southern atoll of the Marshalls for 3 years. In 1957 a new village was built at Rongelap by the U.S. Atomic Energy Commission. The levels of radiation on the island at this time were considered acceptable and the people returned.

Annual examinations by medical specialists from the United States and medical personnel from the Trust Territory of the Pacific Islands have been conducted under the direction of Brookhaven National Laboratory. Some 200 unexposed Rongelap people, away from the island at the time of the accident, have moved back with their exposed relatives and serve as a most satisfactory comparison population.

EARLY FINDINGS

The penetrating gamma radiation dose of 175 rads resulted in temporary anorexia and nausea in the majority of the people with vomiting and diarrhea in a few. Within a few days after exposure the lymphocyte counts showed significant depression and soon reached levels that were one-half or below that of the unexposed comparison populations. The neutrophil counts became similarly depressed reaching a minimum at about 6 weeks post exposure. Platelet levels dropped to one-eighth to one-third normal levels by 30 days. The exposure proved to be sublethal and there were no infections or frank bleeding that could be related directly to observed hematologic changes. No specific therapy was necessary or given for their depression of blood cells.

The deposit of fallout material on the exposed skin surfaces of the people resulted in itching and burning sensations during the first 2 days followed by a development of lesions of the skin at about 2 weeks post exposure. These so-called "beta burns" showed a sequence

of pigmentation, depigmentation and repigmentation. About 90% of the people had these burns but most of them were superficial in nature and healed rapidly. About 15% of the people had deeper skin lesions which have left some degree of scarring and pigment aberrations. Temporary spotty epilation of the head was noted in most people. Though a few benign moles have appeared in areas of severe burns, no evidence of any malignant lesions of the skin has been apparent.

Internal absorption of radioactive material occurred in the Rongelap people as a result of their living in a contaminated environment for the 2 days before their evacuation. They absorbed fission products in the food and water that they consumed. Radiochemical urine analyses revealed the presence of various radioisotopes, chief of which were strontium and iodine (See Table II). The dose to the thyroid gland from radioiodines is discussed in a later section. Except for the thyroid gland the dose to the bone and other organs appeared to have been minimal with no acute effects noted. By 6 months the urinary excretions indicated greatly reduced body burdens. When the people were returned to Rongelap in 1957 a slight residual radioactive contamination of the island resulted in the accumulation of detectable but low body burdens of ^{137}Cs, ^{65}Zn and ^{90}Sr. No effects from these isotopes have been observed.

LATER FINDINGS

Several later findings, prior to the development of thyroid abnormalities, have been noted, some of which may have been related to their radiation exposure. During the 15 years since the accident the exposed people have remained generally in good health (except for thyroid related abnormalities) with no greater incidence of illness or degenerative diseases than that seen in the unexposed populations examined. Though the death rate has been somewhat higher in the exposed people there has been no definite correlation of cause of death with radiation exposure. A somewhat greater percentage of older people in the exposed group partly accounts for this discrepancy. Quantification of a number of recognized aging parameters in order to arrive at "biological age score" have failed to reveal any evidence for premature aging in the exposed as compared with the unexposed people of the same age.

No leukemia has been seen. The occurrence of 3 cases of cancer in the exposed group (1 of the thyroid gland and 2 of the female genital tract) presents a higher incidence in the exposed group, but due to the small numbers of people involved, final decision on this point must await the results of future observations.

Based on birth rates, fertility has been about the same in the exposed as compared with the unexposed population. However about twice the number of miscarriages and stillbirths occurred in the exposed women during the first 4 years after exposure. Fetal abnormalities did not

appear more numerous in the exposed group, though no specific genetic studies have been carried out. A persisting low level of chromosomal aberrations of the type induced by radiation have been noted at 10 years post exposure. Frequent slit lamp observations reveal no increase in opacities of the lens characteristic of radiation exposure.

DEVELOPMENT OF THYROID ABNORMALITIES

Before discussing development of thyroid abnormalities a few words should be said concerning the calculations of the dose to the thyroid. Table II shows the estimates of the various isotopes that were present in the people extrapolated back to day 1 based on radiochemical urine analyses. It can be noted that the largest exposure was to the thyroid gland from radioiodines. In addition to the dose imparted by ^{131}I, the shorter-lived isotopes ^{132}I, ^{133}I, and ^{135}I also contributed substantially to the dose. Absorption of these iodine isotopes was both from inhalation as the radioactive cloud passed over and from drinking contaminated water and eating contaminated food. Based on radiochemical urine analyses beginning at 15 days after exposure it was estimated that about 11.2 μCi of ^{131}I was accumulated in the thyroid gland at the time of the fallout. The adult thyroid was estimated to have received about 160 rads from the radioiodines in addition to 175 rads from whole body gamma irradiation. The dose to the much smaller glands of children was estimated to be considerably higher; in children less than 4 years of age the range was estimated to be 700-1400 rads.

Annual examinations have always included careful thyroid evaluation. [1,2] Until 5 years ago the exposed people were considered to have normal thyroid function with no obvious evidence of any thyroid abnormality. Numerous serum protein bound iodine determinations had been done and all appeared to be in the normal range for these people. We later discovered that Marshallese people in general have high levels of iodoprotein which may have masked an earlier hypothyroid tendency.[3] Dietary and urinary iodine excretion were within the normal range. Serum cholesterol levels had been normal.

Ten years after fallout exposure nodular changes were noted in a 12 year old exposed girl. Since that time increasing numbers of cases of nodularity of the thyroid gland have developed in the exposed people. At the present time there have been 21 cases of thyroid abnormalities, 19 with nodules and 2 other cases with atrophy of the gland with development of marked hypothyroidism. Only 1 of these cases with a nodular thyroid was in the lesser exposed Ailingnae group. Thirty-eight percent of the more heavily exposed group have displayed thyroid abnormalities. This includes one new case that was discovered in March 1969. A notable fact is that 90% of the children exposed at less than 10 years of age have developed such abnormalities. Table III shows the distribution of thyroid cases in the populations under study. Of the 19 children in the 175 rad group exposed at less than 10 years of age, only 2 have failed

to show clearcut abnormality. It is noteworthy that no thyroid abnormalities have been noted in children that received lesser exposure, i.e. the 6 children in the Ailingnae group, the 54 children in the Utirik group and the 48 unexposed children in the same age range. Only 4 cases of abnormalities have been noted in the adults, 1 of these occurring in the lesser exposed group. It should be noted that a low incidence of thyroid enlargement does appear in older people (greater than 50 years of age) of the Utirik and unexposed population (See Table III).

The thyroids of 12 children and 2 adults have been subjected to surgical exploration and the nodules removed. On surgical exposure, the thyroid gland was seen in most cases to be multinodular as shown in Fig. 2. Note the varied size of the nodules from several millimeters to several centimeters, some being cytstic, and some hemorrhagic. The microscopic diagnosis in all but one case was adenomatous goiter. Fig. 3 shows the microscopic appearance with the wide variation in size of follicles closely resembling adenomatous goiter seen with iodine deficiency. Some pathologists claim to see radiation induced changes in the thyroid glands but others do not. Fig. 4 shows the microscopic appearance of the mixed papillary and follicular carcinoma with localized metastases in a lymph node in a 41 year old woman. The histological examinations of the thyroids showed that in the children the tissues surrounding the nodules was usually abnormal while the thyroid tissue surrounding the nodular areas in the two adult cases was relatively normal.

During the recent survey of the Marshallese people in March 1969, it was found that 3 of the cases with nodules who had been exposed at less than 10 years of age had not shown satisfactory response to treatment. In fact 1 case showed a recurrence of a nodule that had previously disappeared in spite of the fact that this subject had supposedly been on thyroid treatment. She complained of a lump in her throat when she swallowed. One new case of nodularity of the thyroid gland was found in a 34 year old woman. These cases will be returned to Brookhaven National Laboratory in the near future for evaluation and possible surgery.

CORRELATION OF THYROID FINDINGS WITH RETARDATION OF GROWTH AND DEVELOPMENT IN EXPOSED CHILDREN

Based on anthropometric measurements and bone age radiographic studies it became apparent several years after exposure that some of the children, particularly boys who had been exposed at less than 12 years of age showed slight degrees of retardation of growth. This was particularly marked in 2 boys who had been exposed at about 15 months of age who were considerably shorter in stature than brothers who were a year younger.[4] It has become increasingly clear that the retardation of growth noted in some of the children is associated with thyroid injury bringing about hypothyroidism. This was not detected in earlier years due to the fact

that the iodoprotein levels, which, as pointed out, in the Marshallese people results in higher than expected PBI levels which masked the true hormone level. However more accurate thyroxine levels during the past several years revealed that the 2 boys showing the greatest growth retardation developed marked hypothyroidism, palpable atrophy of the thyroid gland, development of coarse facial features, dry skin and sluggish Archilles reflex action and bone dysgenesis. High pituitary TSH levels in these two individuals indicated primary hypothyroidism. More recently several other children with lesser degrees of retardation of growth had begun to show some degree of thyroid deficiency prior to surgery. This was based on lowered thyroxine levels, increased levels of TSH, reduced uptake of radioiodine and poor response to TSH stimulation.

In view of the seriousness of the above findings it was decided several years ago to give thyroid hormone therapy to the exposed people. The rationale for this therapy was to furnish normal levels of exogenous thyroid hormone thereby repressing pituitary TSH levels and removing the gland from stimulation of that hormone. Effectiveness of treatment in regard to inhibition of growth of nodules is difficult to evaluate in view of uncertainty of adherence to a strict treatment regimen in some of the people. However the effect on growth and development of the body appears to be encouraging. The two boys who had showed hypothyroidism and the greatest growth retardation showed definite enhancement. Fig. 5 shows the results of hormone treatment in these two boys on development as evaulated by skeletal age. Fig. 6 shows the increased growth and improved appearance of one of these boys following hormone treatment.

DISCUSSION

As a result of the exposure of the Marshallese people to radioactive fallout 15 years ago the only late findings of significance have been the development of thyroid abnormalities with resulting retardation of growth and development in the more heavily exposed children. The lack of development of nodules in the unexposed and lesser exposed populations in the same age range clearly indicates the etiological relationship of the lesions to radiation. The higher incidence of nodules in the children than in adults is probably related to the larger dose of radiation received by their smaller glands. The high incidence of these lesions in this population is perhaps a little surprising in view of the consideration of the dose and dose rate from radioiodine exposure in a fallout situation. [5,6] The fact that a large part of the dose was from short-lived radioiodines with fast dose rate may have been important. The development of these thyroid abnormalities is consistent with reports in the literature on many animal studies and some human studies.[7,8] Sheline et al. [9] have reported the development of nodules in follow-up studies of children for hyperthyroidism with radioiodine and more recently Pincus et al. [10] have reported a high incidence of nodules in children who had been treated with x-radiation of the neck in infancy.

The insidious onset of thyroid hypofunction and retardation of growth in the Marshallese children was probably associated with the slow loss of functioning thyroid cells through lack of replacement due to radiation impairment of cellular replication. One can speculate that less injured cells in the thyroid probably responded to the increased TSH simulation and the picture of concomitant atrophy and hyperplasia resulted in gross nodule formation. In the 2 cases with complete thyroid atrophy, however, there must have been sufficient radiation damage to prevent appreciable responses to TSH stimulation.

No doubt there is increased risk of cancer of the thyroid in the Marshallese children and it is perhaps chance that no such malignancies have yet been discovered. The literature is replete with many retrospective as well as prospective studies which show the late development of cancer of the thyroid in children that had been treated with cervical irradiation during infancy and early childhood.[11-13] However, there is scant evidence as yet for the development of cancer of the thyroid following radioiodine treatment. Increased prevalence of cancer of the thyroid has been reported in adults exposed to the atomic bomb in Hiroshima [14] and other types of radiation.[15] It is of course not possible to prove the causal relationship of irradiation in the case of cancer of the thyroid in the exposed women reported here, but in view of low incidence of such lesions in the Marshallese, this possibility must be seriously considered.

It is not known whether treatment with thyroid hormone will reduce the risk of cancer of the thyroid in the human being. However, such suppression has been reported to prevent the development of thyroid nodules in rats.[16] It is hoped that the hormone treatment being given the Marshallese may suppress such neoplasia from radiation.

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TABLE I

ISLAND GROUPS AFFECTED

Group*	Composition	Fallout observed	Estimated gamma dose(rads)
Rongelap	64 Marshallese	Heavy(snowlike)	175
Ailingnae	18 Marshallese	Moderate(mistlike)	69
Rongerik	28 Americans	Moderate(mistlike)	78
Utirik	157 Marshallese	None	14

*Also exposed were 23 Japanese fishermen aboard their vessel the "Lucky Dragon" who received a sublethal dose.

TABLE II

ESTIMATED BODY BURDEN OF RONGELAP PEOPLE

AT TIME OF FALLOUT

Isotope	Activity(μCi)
^{89}Sr	1.6-2.2
^{140}Ba	0.34-2.7
Rare Earths	0.12
^{131}I(in thyroid gland)	6.4-11.2
^{103}Ru	0-0.013
^{45}Ca	0-0.019
Fissile Material	0.0.16(μgm)

TABLE III

THYROID ABNORMALITIES
IN MARSHALLESE POPULATIONS

Group	Age at Exposure	No. Presently in Group	Gamma Dose(rads)	Estimated Thyroid Dose(I*,rads)	% Abnormalities
Rongelap	<10	19	175	700-1400	90.
Ailingnae	<10	6	69	275-550	0.0
Utirik	<10	54	14	55-110	0.0
Controls	<10	48	0	0	0.0
Rongelap	>10	34	175	160	8.8
Ailingnae	>10	8	69	55	12.5
Utirik	>10	59	14	15	3.4
Controls	>10	133	0	0	2.3

*In estimating the thyroid doses to the Ailingnae and Utirik exposed group, it was assumed that such doses were proportional to the thyroid dose of the Rongelap exposed group, based on relative whole body gamma dose received.

FIGURES

1. Map of fallout area, Marshall Islands, March 1954.

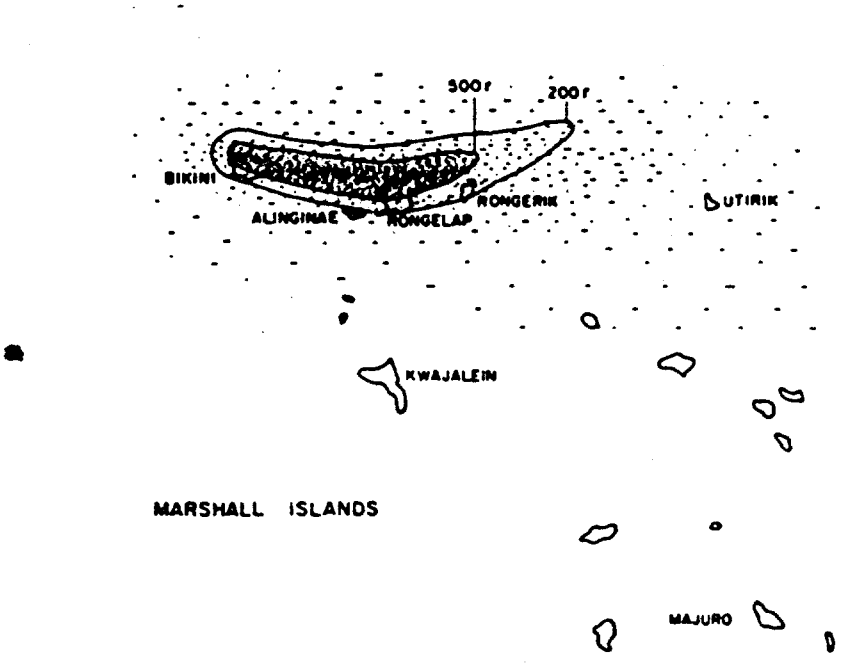
2. Sectioned thyroid gland of 12 year old exposed girl. Note multinodular nature of gland.

3. Microscopic section of benign adenomatous nodule showing wide variation of follicle sizes with cystic changes, atrophy and hyperplasia. (Hematoxylin-eosin X 16)

4. Section showing invasion by metastatic papillary and follicular carcinoma of the thyroid into lymph node. (Case 64) (Elastic X 100)

5. Self-explanatory.

6. On left boy with marked growth retardation and hypothyroidism before thyroid hormone treatment and on right same boy 6 months after treatment started. (No. 3 in Fig. 5)



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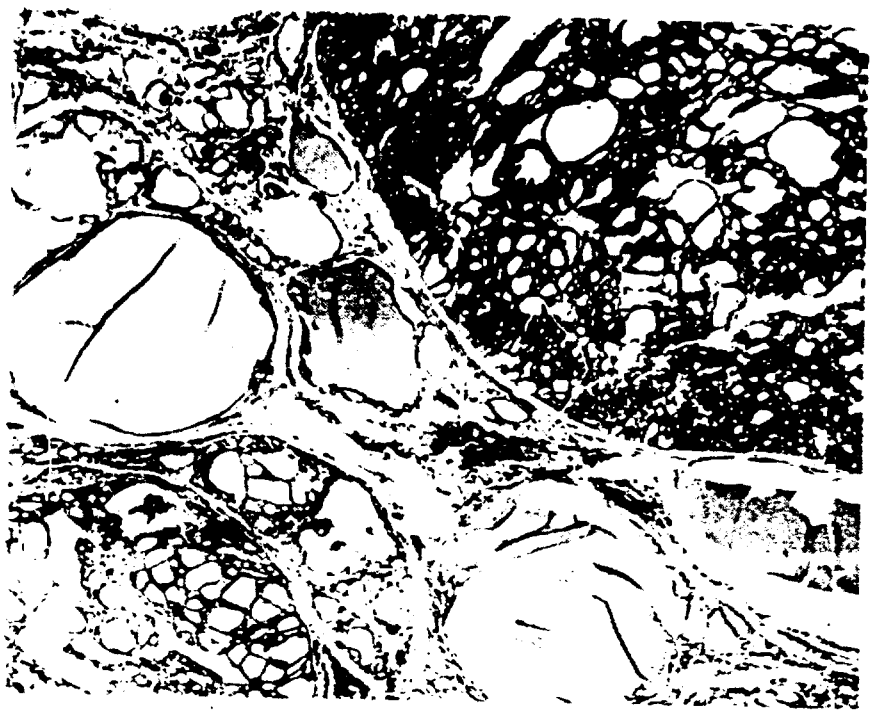

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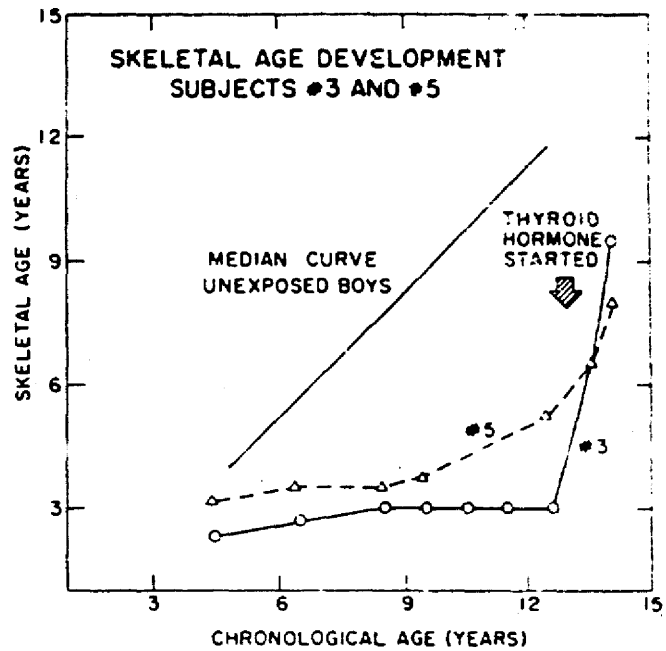

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