Reprinted from the Journal of the American Medical Association
October 12, 1970 Volume 214

1404

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Thyroid Neoplasia as Late Effect of Exposure to Radioactive Iodine in Fallout

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Accidental exposure of people of Rongelap Island to radioactive fallout and particularly to radioactive iodines in the fallout has resulted in the development of thyroid abnormalities in 21 of 67 of these people, 3 with malignant lesions, 16 with benign adenomatous nodules, and 2 with atrophy of the gland with hypothyroidism. The preponderance of lesions occurred in children exposed at less than 10 years of age who had received a greater thyroid exposure. Growth retardation associated with hypothyroid tendency was noted in some children who appear to be responding favorably to thyroid hormone medication. Thyroidectomy, partial to complete, has been carried out on 18 patients. Risk for thyroid cancer from radioactive iodine exposure in this group does not appear to be very different from that reported following x-irradiation.

Thyroid neoplasia developed recently in Marshallese people of Rongelap Island who were accidentally exposed to radioactive fallout in 1954 during the testing of thermonuclear devices in the Pacific proving grounds. During the two days before evacuation 64 people on Rongelap Island received a whole-body gamma dose of about 175 rad and 18 other Rongelap people on a nearby island received about 69 rad. In addition they sustained serious skin exposure and significant internal absorption of radionuclides. A third population on the island of Utirik, 150 miles east of Rongelap, received only a slight exposure and this group will only be referred to briefly in this communication. By 1957 the radioactive contamination of Rongelap Island had reduced sufficiently to allow the people to be returned. At that time a new village was constructed for them. Fortunately more than 200 Rongelap people (relatives of the exposed group) who had not been exposed to fallout returned also and have served as an excellent comparison population.

Annual medical examinations during the past 15 years have documented the acute and late effects of this exposure on these populations.[1-3] The people of Rongelap had early acute signs of exposure including anorexia, nausea, and vomiting followed later by the development of significant but transient depression of the formed elements in their blood. However, no infections or bleeding tendencies were noted and no deaths occurred which could be attributed to radiation exposure. No prophylatic or specific therapy was given. Radioactive contamination of the skin resulted in the development of lesions ("beta burns") and spotty epilation of the head in the majority of the people between two and four weeks following exposure. The skin lesions healed within several weeks and the hair regrew by six months. Some of the people had slight residual atrophy, scarring, and pigment changes of the skin. The acute effects appeared to be more severe in

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the children than in adults. No acute effects of the internal exposure to the radionuclides were noted in the people and the full significance of this exposure was not appreciated at that time.

Until the development of thyroid abnormalities six years ago, only a few possible late effects of exposure were observed in the Rongelap people. These have been described in detail in other reports[1-3] and are only briefly summarized here. During this period the general health of the exposed population remained about as good as that of the unexposed population living on the same island with no illnesses that could be attributed to radiation exposure. A slightly higher death rate was noted in the exposed group but this may have been due to the larger number of older people in that group. Of possible significance has been the continuing slight depression of the mean peripheral blood levels in the exposed population compared with those that were unexposed. About twice the incidence of miscarriages and stillbirths were noted in the exposed women during the first five-year period but general fertility in the exposed people appears to have been about the same as that in the unexposed based on the number of live births. No malignant lesions of the skin and no cases of leukemia have developed. Two cases of cancer of the female genital tract in exposed women compared to none in the unexposed group have occurred. Attempts to quantify aging changes did not indicate any premature aging effects in this exposed population. Studies of chromosomes and peripheral blood cultures of the Rongelap people ten years after exposure indicated that small numbers of chromosome aberrations of the type usually associated with radiation exposure were still present.

One of the more important findings noted within a few years after radiation exposure was slight retardation of growth in some of the exposed children as evidenced by extensive anthropometric measurements and skeletal maturation studies. The retardation of growth was most notable in boys who had been exposed when less than five years of age, particularly in two boys exposed between 15 and 18 months of age.[3]

Thyroid Lesions

Estimations of Radiation Dose to the Thyroid Gland.—Unfortunately the calculations of dose to the thyroid from the absorption of radionuclides in the fallout had to be based on radiochemical urine analyses that were obtained several weeks after the accident. It was known that there were several isotopes of iodine in abundance in the fallout (^{131}I, ^{132}I, ^{133}I, ^{135}I). These iodine isotopes gained entry into the body from inhalation and from consumption of contaminated food and water during the two days before the people could be evacuated from the island. It was calculated that the thyroid gland on the average accumulated roughly 11.2 microcuries of ^{131}I on the first day of exposure. The extrapolated dose to the adult thyroid of the people on Rongelap was 160 rad from all the radioactive iodines plus 175 rad from gamma radiation. Due however, to the smaller size of the thyroid gland in children and to other factors it was estimated that the thyroid of a 3- to 4-year-old child received 700 to 1,400 rad from radioactive iodines in addition to 175 rad of gamma radiation. In view of thyroid atrophy that developed in two boys it must be conceded that the doses to the thyroid in these two patients must have been considerably higher.

Early Thyroid Studies

Even before the development of thyroid nodules was noted the evaluation of thyroid status of the exposed individuals received considerable attention since it was recognized that the slight growth retardation noted in some of the children might be related to radiation effects on that gland. However, based on physical examinations and serum protein-bound iodine (PBI) and cholestrol determinations each individual examined was believed to be euthyroid. Later, studies of serum iodines indicated that the Marshallese normally possess higher levels of iodoproteins than is usually found in other populations. Thus, the higher-than-expected PBI values in some patients may have obscured incipient thyroid deficiency at the time of early observations.[4]

Development of Thyroid Lesions

Nine years after the accident an asymptomatic thyroid nodule was detected during routine annual physical examination in a 12-year-old girl and the following year, two 13-year-old girls who had been exposed were also found to have nodules of the gland. Since then, increasing numbers of thyroid abnormalities have appeared in the exposed Rongelap people. In 19 people nodularity of the gland has been the prominent finding while in two additional boys atrophy of the gland has developed. The nodules were usually multiple, nontender, and varied in consistency. In some instances enlargement of one or both lobes was noted. Surgical exploration, to be described, has been carried out in 18 of the 19 nodular thyroid glands. Benign adenomatous lesions were found in all with the presence of malignant lesions also present in three of these patients. One adult with somewhat less significant nodularity of the thyroid is still under observation. In view of the seriousness of these developments in the thyroid a panel of ex-

1. Excised thyroid showing nodular nature of gland.

2. Autoradiogram of section made through nodule of thyroid with benign lesions. Lack of grains (superimposed blackening) *shows adenoma in center is nonfunctioning (hematoxylin-eosin stain, ×14).*

perts advised that the people be given supplemental thyroid hormone. This treatment was instituted in September 1965.

The Table outlines the incidence of benign nodules (including atrophy of the gland), the malignant lesions, and the estimated dose of radiation to the thyroid glands in the various populations under study. The highest incidence of thyroid lesions (89.5%) has been noted in the heavily exposed Rongelap children who were less than 10 years of age at the time of the accident. The absence of lesions in children of the same age in the lesser exposed and unexposed groups is most notable. The incidence of thyroid lesions in the adults of the more heavily exposed group is considerably lower than in the children but is significantly higher than is generally seen in the adult population of the lesser or unexposed groups. (Only one individual has been found to have an adenomatous thyroid lesion in the lesser-exposed Rongelap group.)

The first case of carcinoma of the thyroid was discovered in 1965 in a 40-year-old woman in the heavily exposed group, 11 years after exposure. At that time the relationship of radiation exposure to the appearance of this lesion was seriously questioned, although such lesions are rare in the Marshallese. However, in September 1969 surgical exploration of the thyroid on five Marshallese with palpable nodules revealed malignant lesions in three additional people. Two of the malignant lesions occurred in women in the more heavily exposed Rongelap group, one in a 36-year-old woman who was 21 years of age at exposure and one in a 22-year-old woman who was 7 years of age at the time of exposure. This latter patient presents the first malignant thyroid lesion to be noted in the group of heavily exposed children who have the highest incidence of benign lesions. These recent findings greatly increase the concern about radiation-induced neoplasms in this population. The fourth malignant lesion was noted in a woman from Utirik Island.

3. Section of thyroid showing two benign papillary adenomas (hematoxylin-eosin stain, ×14).

4. Multiple clusters of what appear to be atypical proliferating cells in thyroid which contains several large discrete adenomas. Lesions were considered benign (hematoxylin-eosin stain, ×20).

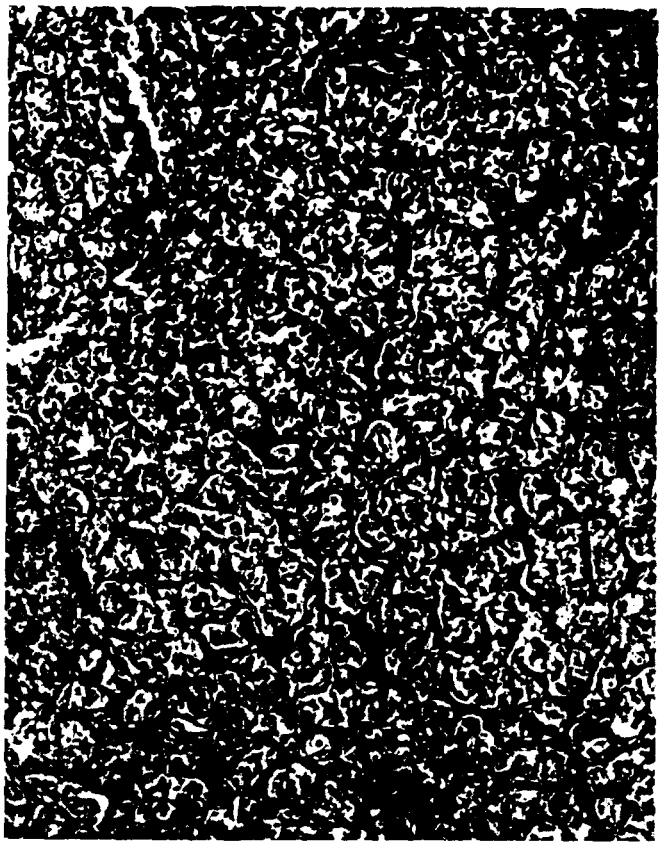
Surgical Exploration of Thyroid Nodules

Thyroid operations have been performed at the following times: three in 1964, three in 1965, five in 1966, three in 1968, and five in 1969.

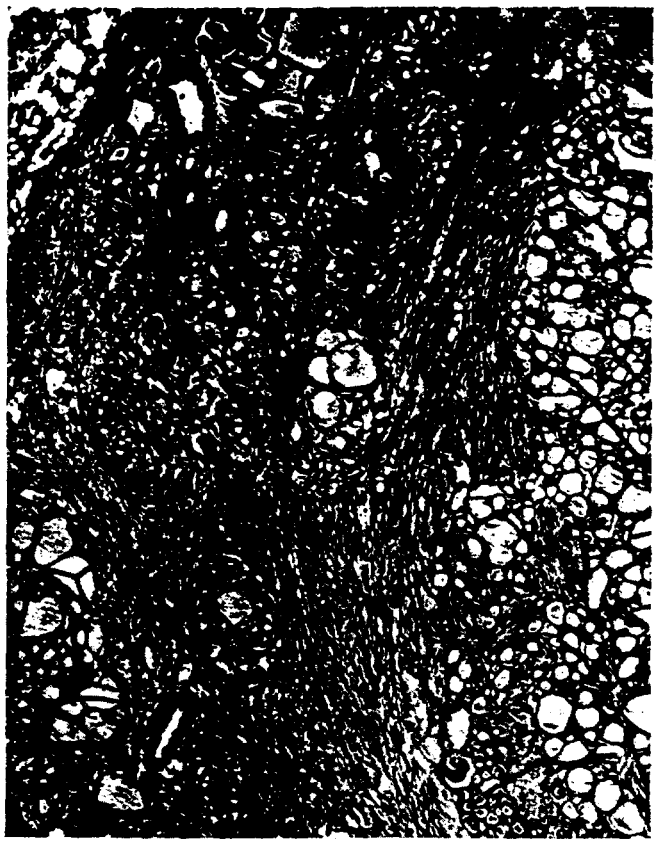
At surgery the gross appearance of most of the thyroids were lobulated but in addition contained grossly discrete masses (Fig 1). The benign thyroid lesions exhibited multiple nodules varying in size from a few millimeters to several centimeters. They varied from soft to firm in consistency, and were hemorrhagic or in many instances cystic. It was noted in some that there was increased fine vascularity over the surface of the gland similar to that which has been noted in thyroids which had been treated with large doses of ^{131}I for hyperthyroidism. Some of the recent patients had received small tracer doses of radioactive iodine the day before surgery so that the nodular tissue could be measured for radioactive content at the time of surgery. The discrete lesions in many instances showed ^{131}I uptakes which were different from the extra nodular tissue. Most of the discrete benign lesions showed less uptake than the extra nodular surrounding tissue (Fig 2). Measurement of radioactive iodine in the malignant tissue was found to be nil when it was compared with the surrounding more normal tissue.

Microscopic examination of the benign lesions revealed marked variation in size of follicles. The cells of some follicles appeared atrophic, while others were hyperplastic, which was reminiscent of iodine deficiency goiter (Fig 3). In addition to the gross adenomatous masses in the 15 thyroids which were classified as benign there were multiple microscopic clusters of what appeared to be atypical proliferating cells here and there in the parenchyma of some of these thyroids (Fig 4 and 5).

Microscopically the thyroid carcinomas were considered of low-grade malignancy and varied in structure from papillary to mixed



5. Area of atypical proliferating cells in thyroid which had developed multiple discrete benign adenomas (hematoxylin-eosin stain, ×70).



6. Follicular carcinoma of thyroid showing capsular invasion in 35-year-old woman exposed to fallout. This represented discrete mass as shown in Fig 4. No lymph node metastasis (hematoxylin-eosin stain, ×26).

papillary and follicular type. All showed invasion of the thyroid capsule and in two patients localized metastases to lymph nodes were present and in two other patients blood vessel invasions were noted (Fig 6 and 7). Benign adenomatous changes accompanied malignant changes in the glands. Total thyroidectomies were performed in three patients with malignancy, and a left radical cervical lymph node dissection was carried out in one of these patients because spread to lymph nodes was seen. The fourth patient had a hemithyroidectomy. No metastases have been recognized beyond the cervical region in any patients.

Thyroid Functions; Correlation With Retardation of Growth in Children

In some children with thyroid lesions, deficiency in serum thyroxine has been correlated with retardation of growth. The most striking instances of hypothyroidism were in two boys who showed marked retardation of statural growth and bone age. By 1964, they had developed obvious atrophy of the thyroid gland with almost complete loss of thyroid function as evidenced by a failure of the thyroid to take up much, if any, iodine even after thyroid-stimulating hormone (TSH) stimulation. By this time there were low thyroxine and very high TSH levels in the blood. The boys showed bony dysgenesis, sluggish Achilles tendon reflexes, puffy faces, and dry skin. The patients' response to thyroid hormone supplement as evidenced by growth spurt, improved appearance, etc, has been dramatic (Fig 8 and 9). Several other children who displayed thyroid nodularity and whose statural growth was below average showed low or low-normal serum thyroxine values and poor radioactive iodine uptake after TSH stimulation which indicated that their thyroid glands were functionally impaired and were operating near their maximum capacity. Functional deficiency of the thy-

7. Papillary carcinoma demonstrating extensive connective tissue invastion within lobe. Patient had multiple cervical lymph node metastasis (hematoxylin-eosin stain. ×64).

8. One of two boys who have developed myxedema. Left, *At 12 years of age at beginning of treatment with thyroid hormone.* Right, *Marked growth and improvement in appearance after three years of treatment.*

roid was not demonstrated in adults with nodules or with carcinoma of the thyroid.

Influence of Physiological Stress on Thyroid Abnormalities

An assessment was made of the relationship of the development of puberty to the occurrence of thyroid nodules. Degrees of pubescent changes have been recorded annually by a grading system. The two boys that showed greatest retardation of growth had developed atrophy of the thyroid gland before puberty. Here changes associated with puberty were delayed. There may be some association between the apparent increased demand for thyroid hormone at puberty and the

Thyroid Lesions in Marshallese, March 1969

Island Group (Radiation Dose-Gamma)	Age at Exposure (yr)	Estimates Thyroid Dose (Rad, Radioactive Iodines*)	Thyroid Lesions (%)†	Malignant Lesions (%)†
Rongelap (175 Rad)	<10	500-1,400	89.5 (17 of 19)	5.3 (1 of 19)
	>10	160‡	8.8 (3 of 34)	5.9 (2 of 34)
	all	...	39.6 (21 of 53)	5.7 (3 of 53)
Rongelap (69 Rad)	<10	275-550	0.0 (0 of 6)	...
	>10	55	12.5 (1 of 8)	...
	all	...	7.1 (1 of 14)	...
Utirik (74 Rad)	<10	55-100	0.0 (0 of 40)	...
	>10	14	5.1 (3 of 59)	1.7 (1 of 59)
	all	...	3.0 (3 of 99)	1.0 (1 of 99)
Rongelap (unexposed)	<10	...	0.0 (0 of 61)	...
	>10	...	2.3 (3 of 133)	...
	all	...	1.5 (3 of 194)	...

Dose from ^{131}I, ^{132}I, ^{133}I, ^{135}I.
†Based on number now living.
‡Children 10 to 20 years of age at exposure received doses between 160 and 500 rad

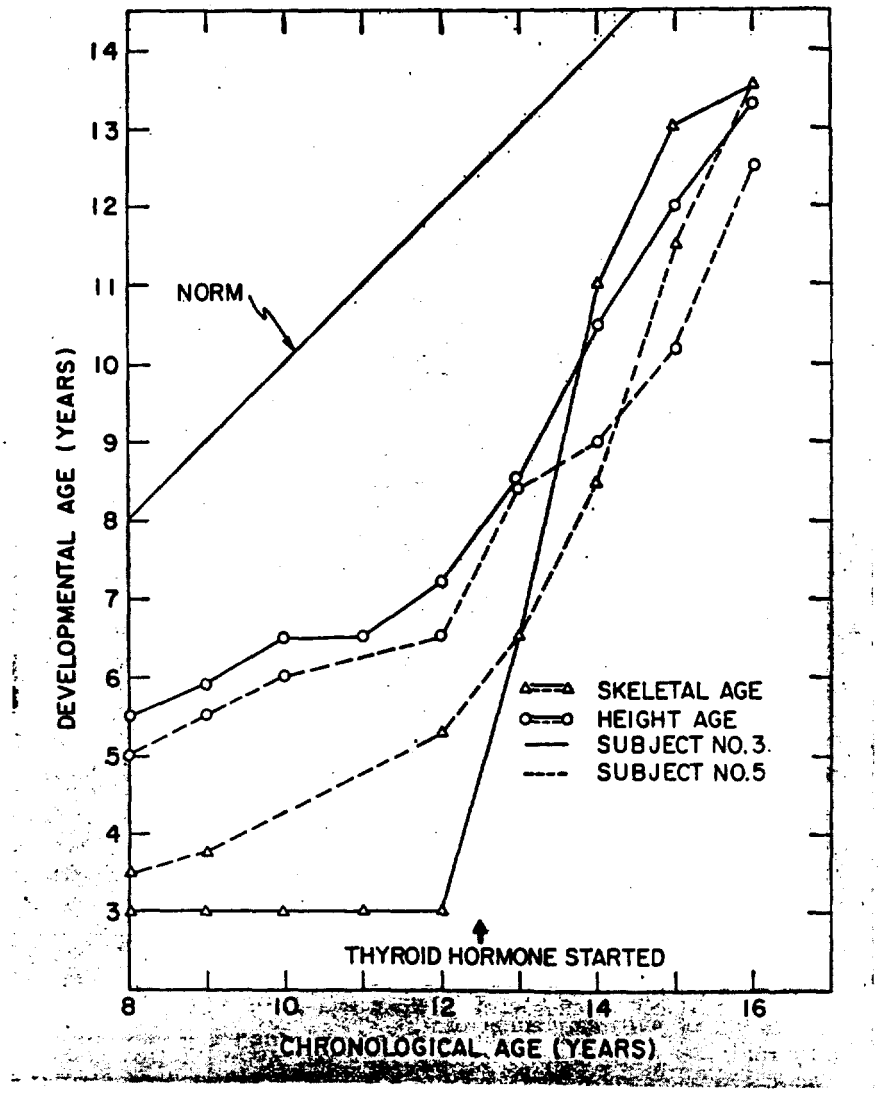
appearance of thyroid nodules since in ten children thyroid nodules appeared near the expected or actual time of puberty. In five other children (two boys and three girls) in this group, the nodules appeared one to three years after puberty and in the girls were associated with pregnancies. In evaluating the influence of puberty and pregnancy it should be pointed out that the latent period between exposure and the development of thyroid abnormalities was fairly constant in all of these children, varying between 10 and 13 years, so that these findings may have been fortuitous. In the four women who developed carcinoma of the thyroid the possible influence of the stress of pregnancy must be considered since all had multiple pregnancies in the years preceding the development of lesions.

Sex Incidence

The sex ratio of benign thyroid lesions occurring in the Rongelap population was females 1.3 to males 1.0. The findings may be misleading since all of the females in the group exposed at less than 10 years of age had lesions whereas two males in the group did not. The fact that all three malignant lesions of the thyroid were in females is consistent with reported statistics showing preponderance of such lesions in females.[5]

Comment

At the time of appearance of the first malignant thyroid lesion in the more heavily exposed Rongelap group several years ago numerous benign adenomatous thyroid nodules had appeared which were suspected of being related to the radiation exposure. However, such an etiological relationship to the single isolated malignant lesion found at that time was speculative. With the findings of two aditional individuals with thyroid carcinoma in this group (three among 21 thyroid lesions in 67 Rongelap people exposed) makes the etiological role of radiation exposure increasingly probable. It seems less likely that the single malignant lesion found in the thyroid of the woman from Utirik is due to radiation exposure because of the low dose of radiation received by the people from that atoll.



9. Relative patterns of skeletal maturation and statural growth (connected to developmental ages) in two boys who had marked hypothyroidism. Comparison is with unexposed boys. Note dramatic change in slope of growth curves after thyroid hormone administration.

The significance of radiation exposure of the thyroid glands in the Rongelap people had not been fully appreciated until the actual appearance of thyroid lesions. More care-

ful review of the dose calculations indicated that considerable exposures from radioactive iodine absorption had probably occurred particularly in the children. The exposure of the Rongelap people was not comparable to exposure of populations from fallout from reactor accidents where radionuclides are chiefly absorbed from contaminated milk obtained from cattle grazing on contaminated pastures. In the Marshall Islands there are no cattle and no local milk supply. (Mother's milk may have contributed to the radioactive iodine absorption in two children who were reported to have been nursing at the time of the accident). But there was heavy contamination of food and water supplies on Rongelap and a relative abundance of radioactive iodines in the fallout. The dose to the thyroid glands was greater by a factor of 2 in adults and a factor of about 7 in children over that to other organs of the body.

Numerous animal studies have demonstrated the role of radiation in the etiology of thyroid neoplasms.[6-8] In the human being the development of thyroid nodules and cancer form x-irradiation,[9-10] particularly when the radiation of the gland occurs in infancy and childhood[11-13] is well documented. Development of such lesions from radioactive iodines has also been seen in animals but has been less frequently observed in human beings. Eight patients with nodular goiter have been reported by Sheline et al[9] in their follow-up study of 250 patients treated for hyperthyroidism. Six of these patients were irradiated before 20 years of age and four before 10 years of age. One patient showed a possible invasion of the thyroid capsule.

The incidence of thyroid nodularity in the exposed Marshallese (based on the number of exposed people now living) is considerably higher than has been reported by Pincus et al[11] and Hempelmann[13] in their studies of populations who had been exposed to therapeutic x-irradiation of the neck region at a young age. However, when comparison is made on a risk-per-rad basis the incidence is quite comparable with 51 cases per 10^6 persons per rad per year for the Marshallese and 24 cases for one group and 64 for a second group 10^6 persons per rad per year calculated by Pincus et al and Hempelmann. This comparison seems to indicate similar effectiveness per rad of x-radiation compared with per-rad dose from radioactive iodine exposure.

The three malignant lesions of the thyroid reported here in the heavily exposed Rongelap people appear to be the first such cases clearly associated with radioactive iodine exposure with the exception of the one possible malignant thyroid lesion reported by Sheline et al.[9]

Based on the Trust Territory records of incidence of carcinoma of the thyroid among the 17,000 Marshallese, the expected incidence in the original 64 Rongelap people in the high-exposure group would be 0.056 cases over the 15-year period. The finding of three cases thus represents a considerable increase over the expected number of cases ($P > 0.01$, chi square test). Among the 157 Utirik people about 0.14 cases would be expected with 1 case reported. It seems less likely that this single isolated case among the Utirik people would involve radiation etiology in view of the low dose received by this group and the fact that no nodular lesions had been noted among the children. Based on the present incidence of thyroid malignancy in the high-exposure Rongelap group (based on the number of exposed people now living), the risk for development of this malignancy per 10^6 persons per rad per year is three cases for the children exposed at less than 10 years of age, ten cases for the older people, and 5.6 cases for the group as a whole. The risk in the Marshallese children is not inconsistent with that reported by others.[13]

It has been generally believed that radioactive iodine exposure was less effective than x-radiation in producing thyroid lesions based primarily on the fact that few thyroid tumors had been noted following radioactive iodine therapy.[5] It seems likely, however, that the scarcity of such findings is relative to the high doses of radiation used (5 to 10,000 rad or more in the treatment of hyperthyroidism and 50,000 rad or more for ablation of the gland to ameliorate symptoms in certain diseases). Such doses probably are so destructive that they preclude proliferative activity and malignant transformation in such damaged glands. The increasing incidence of hypothyroidism without tumor formation, years after treatment of hyperthyroid patients with radioactive iodines illustrates this point.[14] It has been shown that tumor formation in animals is not always a dose-dependent phenomenon.[15] Shellabarger et al[16] showed that breast tumors in rats reached a maximum incidence at about 400 rad and the occurrence of neoplasms fell off with higher doses. Lindsey and Chaikoff[8] reported that doses of ^{131}I in rats in excess of 200 to 400 microcuries were less carcinogenic than lower doses. Marks and Bustad report similar findings in sheep.[17] Though the dose to the thyroid gland in the Marshallese was generally considerably below the dose of ^{131}I used for therapy of hyperthyroidism it is likely that the doses received by some of these children were in excess of the optimum carcinogenic range and, therefore, the true risk per effective rad may be greater in this group. The paradoxical finding of greater risk

in the older group appears to be in line with this reasoning. The cases of two stunted Marshallese boys who showed almost complete atrophy of their thyroid glands with no evidence of nodular development are probably comparable to those cases of hypothyroidism developing in patients years after receiving radioactive iodine therapy. It should be pointed out that the thyroid exposures in the Rongelapese were slightly different from patients treated with ^{131}I because their thyroids were not hyperplastic when exposed and at least part of the radioactive iodine isotopes to which they were exposed were of shorter half life than ^{131}I. In addition their exposure was complicated by gamma radiation.

There were some factors secondary to radiation exposure that might have enhanced the development of thyroid lesions in the Marshallese. Iodine deficiency or presence of goitrogens in the diet did not appear to be among these. However, the physiological stresses of puberty and pregnancy may have played a role in the development of the lesions. For instance the development of ten cases of nodular goiter in the children during or near the time of puberty might indicate that this stress may have enhanced nodular development. In three women who developed thyroid nodules later the demand of multiple pregnancies may have been related. However, since the latent period between exposure and nodule discovery varied only between 10 and 13 years it may be argued that development of thyroid nodules was independent of these stresses. On the other hand it is noteworthy that all of the women who developed malignant thyroid lesions had multiple pregnancies prior to the appearance of such neoplasms.

The development of thyroid nodules in the Marshallese showed only a slight preponderance in favor of the women (1.3 to 1.0). This is similar to the near equal sex ratio reported by Toyooka et al[12] for thyroid nodules developing in persons irradiated over the neck region in infancy. However, in the case of carcinoma of the thyroid the expected female preponderance occurred.[5]

The insidious development of growth retardation in some of the Marshallese children before clinical evidence of thyroid abnormality or deficiency was recognized demonstrates the apparent sensitivity of growth and developmental processes to borderline or subclinical thyroid deficiency. All possible steps are being taken so that the children will adhere to the present thyroid treatment schedule so that they will achieve satisfactory growth and maturation.

Careful medical surveillance of these exposed people including those on Utirik will be essential in future years. The latent period for the development of cancer was 7 years in one case and 14 and 15 years in the other two. The fact that there may be a longer latent period for the induction of malignant change is borne out by a report by Goolden who noted the development of thyroid cancer 40 years after radiation exposure.[18] It may be that we are just reaching the critical period in the postradiation observations.

This investigation was supported by the US Atomic Energy Commission.

Keith Thompson, MS, assisted in carrying out statistical analyses.

CAPT Carl A. Broaddus, Jr., MC, USN; Bentley P. Colcock, MD; and Brown M. Dobyns, MD, performed the thyroid operations.

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