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Original Contributions

Thyroid Hypofunction After Exposure to Fallout From a Hydrogen Bomb Explosion

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• Thyroid function was evaluated in the Marshallese who were accidentally exposed to fallout-containing radioiodine isotopes in 1954. Measurements of thyrotrophin (TSH, thyroid-stimulating hormone) levels and free thyroxine (T_4) index (FT_4I) have revealed that, among 86 persons exposed on Rongelap and Ailingnae atolls, 14 have shown evidence of thyroid hypofunction. This was first noted in some individuals about ten years after exposure. Only two of these showed clinical evidence of hypothyroidism. The most marked TSH elevations were noted in nine persons exposed when younger than 6 years, with estimated doses to the thyroid from 390 to 2,100 rad. Most of this group subsequently had surgery for removal of thyroid nodules. The remaining five cases have been noted more recently among 36 surviving adults exposed at an older age who showed no other detectable thyroid abnormalities. This group had received estimated thyroid doses ranging from 135 to 335 rad and showed modest elevation of serum TSH levels (6 to 9 μU/mL) and a slightly subnormal FT_4I. No abnormalities were found in persons on Utirik who received substantially less radiation, and hypothyroidism was present in less than 1% of the control, unexposed Marshallese. The high prevalence of a thyroid hypofunction in these persons indicates that this condition, as well as thyroid nodularity, can be a delayed complication of exposure to early fallout from a nuclear explosion. The fact that a significant fraction of the radiation to the thyroid was from short-lived radioiodine isotopes (^{132}I, ^{133}I, ^{135}I), as opposed to ^{131}I, may account for the severity of the thyroid damage.

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THE CIRCUMSTANCES surrounding the accidental exposure of 250 Marshallese people to fallout after the detonation of an approximately 15-megaton thermonuclear device at Bikini Atoll in 1954 have been summarized previously.[1-3] Because radioactive isotopes of iodine were present in the fallout, a careful survey of these persons for potential thyroid abnormalities has been performed on a regular basis since that time. Thyroidal complications were first recognized about ten years after exposure, when both primary hypothyroidism and thyroid nodules were discovered.[1-3] Benign and malignant thyroid tumors are an expected complication of thyroid radiation, particularly in young people.[4-8] Obvious clinical hypothyroidism was detected in two of the children about ten years after exposure, and it was thought initially that these were the only two persons so affected.[1-3] With current laboratory techniques, it has been possible, both retrospectively and prospectively, to evaluate others of the exposed group for thyroid dysfunction.[9] The present report summarizes the results of these studies, which indicate that, in addition to neoplasia, hypothyroidism is a complication that has occurred in a significant fraction of this population.

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METHODS

Several types of thyroid function testing were performed during the annual or semiannual visits of the Brookhaven National Laboratory (Upton, NY) medical team to the Marshall Islands. Most of these tests have been of a prospective nature, and a limited number were retrospective.

Retrospective Analyses

Fortunately, some unused samples of plasma obtained for thyroxine (T_4) measurements as long ago as 1963 had been preserved in a frozen state at Brookhaven National Laboratory. These samples were analyzed using the following tests: plasma T_4, thyroxine-binding globulin index (TBGI, a normalized triiodothyronine [T_3] charcoal uptake), and plasma thyrotrophin (TSH, thyroid-stimulating hormone).[10,11] While the stability of TSH under these circumstances is not known, one sample from 1963 had a TSH concentration of 500 μU/mL, suggesting that such measurements are reasonable. The free thyroxine index (FT_4I) was the product of the T_4 and TBGI. The normal ranges for these determinations in the US population are as follows: plasma T_4, 5 to 10.2 μg of T_4 per deciliter; TBGI, 0.85 to 1.10 units; FT_4I, 4.7 to 9.7 units; and plasma TSH, less than

1 to 6 μU/mL. Antithyroid microsome and antithyroglobulin antibodies were measured using commercial kits.

Prospective Studies

Plasma T_4, TBGI, and TSH levels were evaluated regularly in persons who had had thyroid surgery and who were receiving levothyroxine sodium replacement therapy. In persons not operated on, prophylactic levothyroxine sodium replacement was discontinued for a period of two to four months, and baseline thyroid function studies, a thyrotrophin-releasing hormone (TRH, protirelin) stimulation test (500 μg of protirelin intravenously [IV] followed by a plasma TSH measurement 20 minutes later), and, in some persons, a TSH stimulation test (10 units of bovine thyrotrophin given intramuscularly [IM] followed by a plasma T_4 measurement 24 hours later) were performed.

Thyroid Dosimetry

Rongelap and Ailingnae are about 100 nautical miles east of the detonation site on Bikini, and fallout began on these two islands four to six hours after the explosion. Utirik is 175 miles further east, and the fallout appeared there 22 hours after the detonation. The Marshallese were evacuated from these three islands about 48 hours after the fallout first appeared. The dose to the thyroid of the Rongelap people was estimated from the ^{131}I in a pooled urine sample collected 15 days after the exposure.[11] The amount of ^{131}I in the thyroid of these subjects on the first day of fallout was estimated to be 11.2 μCi (5.6 to 22.4 μCi), assuming that 0.1% (range, 0.05% to 0.2%) of the maximum thyroidal ^{131}I was excreted in the urine on the 15th day.[11] The quantities of shorter-lived iodine isotopes (^{132}I half-life [t½], 2.5 hours; ^{133}I t½, 21 hours; and ^{135}I t½, 6.7 hours), which are produced in the initial fission process, could not be measured. The dose to the thyroid from these isotopes was calculated to be as much as three times that received from ^{131}I.[11]

The thyroid dose to the Rongelap adult (including external γ radiation) was estimated to be 335 rad (220 to 450 rad) (Table 1). Because of the smaller size of the thyroid gland in children, the dose due to a given quantity of thyroid radioiodine was larger than in adults.[11] A 3-year-old child was thought to have received a thyroid dose of 700 to 1,400 rad, and a 1-year-old, 2,000 or more rad. In addition to the variables of gland size, and the prevalence of short-lived isotopes of iodine, a major uncertainty is in the quantity of radioactive iodine ingested by different individuals from contaminated food and water during the two days before their evacuation. All subjects received total-body irradiation from external sources that ranged from 14 rad on Utirik to 175 rad on Rongelap (Table 1). These estimates of γ exposure have been thought to be reasonably accurate, since the observed hematologic depression in the Rongelap people was in general agreement with what would have been predicted.[13]

Table 1.—Thyroidal Radiation Dose Estimates and Thyroid Nodularity, Exposed and Control Marshallese Population, 1979

Age at Exposure, yr (1954)	n	Estimated Thyroid Dose, Rad	No. of Subjects Having Surgery for Benign or Malignant Thyroid Nodules
Rongelap (whole-body γ dose, 175 rad)			
<10	22(3)*	390-2,100	17
10-18	12	335-810	2
>18	33	353	5
Ailingnae (whole-body γ dose, 69 rad)			
<10	7(1)*	275-450	2
10-18	1	190	0
>18	11	135	3
Utirik (whole-body γ dose, 14 rad)			
<10	64(8)*	60-90	2
10-18	21	30-60	3
>18	79	30	8
Unexposed			
<10	212	...	6
10-18	60	...	5
>18	337	...	9

*Numbers in parentheses indicate persons exposed in utero.

RESULTS

Normal Values for Thyroid Function Tests in the Marshallese Population

The plasma TSH concentration in the control Marshallese population is presented in Table 2. In 115 unexposed persons who were clinically euthyroid, 11 subjects had a plasma TSH concentration greater than 3 μU/mL. Only one of these was greater than 6 μU/mL. This person was a 59-year-old woman (subject No. 982) whose plasma TSH concentrations over the past five years have ranged between 6 and 7 μU/mL, and whose most recent plasma T_4 level was 6.4 μg/dL; TBGI, 0.76 units; and FT_4I, 4.9 units. Antimicrosomal and antithyroglobulin antibodies were not detected. Evaluation of samples obtained from 99 Utirik subjects exposed to low levels of radiation showed that a similar fraction (12%) had plasma TSH concentrations in excess of 3 μU/mL, but none was greater than 6 μU/mL. On the basis of these data, a value of 6 μU/mL or greater was considered abnormal in the Marshallese population. In 12 unexposed, euthyroid Marshallese, protirelin infusion studies were performed. The plasma TSH 20 minutes after IV infusion of 500 μg of protirelin was 10.8±4.7 μU/mL (SD) higher than the basal level. Ten euthyroid unexposed Marshallese were given 10 units of thyrotrophin IM and their plasma T_4 levels were measured 24 hours later. The mean initial plasma T_4 concentration in this group of ten subjects was 6.0±1.7 μg/dL, and the mean T_4 increment after introduction of thyrotrophin was 4.2±1.3 μg/dL.

Table 2.—Plasma TSH Concentrations in the Marshallese Population*

	n	TSH Level >3 μU/mL	TSH Level ≥6 μU/mL
Control unexposed	115	11	1
Utirik exposed	99	12	0

*Samples obtained between 1975 and 1979. TSH indicates thyrotrophin (thyroid-stimulating hormone).

Thyroid Function After Thyroid Surgery

In the last column of Table 1 are shown the numbers of subjects who have had thyroid surgery (usually subtotal thyroidectomy) for benign or malignant thyroid nodules. During the period 1972 to 1974, plasma TSH concentration was greater than 6 μU/mL (range, 6.2 to 460 μU/mL) in 11 of 20 Rongelap persons who had surgery despite the prescribed levothyroxine sodium replacement. The number of subjects in whom the residual thyroid function was inadequate was higher than expected. This suggested that

Table 3.—Tests of Thyroid Function in Exposed Marshallese With Evidence of Thyroid Dysfunction*

Subject No./ Age at Exposure, yr/Sex	Estimated Thyroid Dose, Rad	Age at Surgery for Thyroid Nodules, yr	Age Hypothyroidism Recognized, yr†	T_4, μg/dL (5-10.2)‡	TBGI, Units (0.85-1.10)‡	FT_4I, Units (4.7-9.7)‡	TSH, μU/mL (<6)‡
3/1/M	1,050-2,100	...	10	2.5§	0.95§	2.4§	69§
5/1/M	1,050-2,100	...	10	0.4	0.71	0.3	500
33/1/F	1,050-2,100	13	13	8.3	0.82	6.8	22
65/1/F	1,050-2,100	13	13	1.9‖	...	...	...
2/2/F	700-1,400	13	12	6.5	0.84	5.5	22
69/4/F	700-1,400	15	14	1.4	0.64	0.9	470
19/5/M	390-780	19	14	5.7	1.01	5.8	8
83/in utero (≈6-mo gestation)¶/M	>175	20	20	3.3	0.98	3.2	7

*Before thyroid surgery or treatment for clinical hypothyroidism.
†Usually corresponds to the earliest abnormal plasma thyrotrophin measurement.
‡95% confidence interval. T_4 indicates thyroxine; TBGI, thyroxine-binding globulin index; FT_4I, free thyroxine index; TSH, thyrotrophin (thyroid-stimulating hormone).
§Plasma obtained in 1977, when levothyroxine sodium therapy had been discontinued by the patient.
‖Thyroxine iodine (T_4I) (normal range, 3.0 to 6.4 μg/dL).
¶Mother had an estimated thyroidal dose of 425 rad.

Table 4.—Thyroid Function in Exposed, Unoperated-on Marshallese With Evidence of Mild Thyroid Dysfunction

Subject No./ Age at Exposure, yr/Sex	Estimated Thyroid Dose, Rad	Age Recognized, yr*	T_4, μg/dL (5-10.2)†	TBGI, Units (0.85-1.10)†	FT_4I, Units (4.7-9.7)†	Increment After TSH, μg of T_4/dL (4.2±1.3) (SE)	TSH, μU/mL	
							Basal (<6.0)	20 min After TRH (8.4-18.2)†
32/3/M	700-1,400	29	5.1	0.89	4.5	...	6.7,7.3	...
4/38/M	335	58	5.4	0.82	4.4	0.9	6.0,7.0	25
71/27/F	335	51	4.1	1.04	4.3	...	6.5,7.0	35
78/37/F	335	63	4.5	0.89	4.0	0.8	6.1,8.8	88
34/45/F	335	69	4.8	0.80	3.8	0.2	6.3,8.3	48
16/39/M	135	62	4.2	1.00	4.2	0	6.4,6.5	24

*Usually corresponds to the date of earliest abnormal plasma thyrotrophin (TSH) (>6 μU/mL) measurement.
†95% confidence interval of the response in euthyroid Marshallese. T_4 indicates thyroxine; TBGI, thyroxine-binding globulin index; FT_4I, free thyroxine index; TRH, thyrotrophin-releasing hormone (protirelin); TSH, thyrotrophin (thyroid-stimulating hormone).

thyroid dysfunction might be a more common problem in these persons than was appreciated initially and led to the broader studies described hereafter.

Retrospective Analyses of Thyroid Function in Frozen Serum Samples

A limited number of frozen plasma samples were available that were obtained before surgery. Until 1968, the determination of T_4 levels was dependent on the protein-bound iodine (PBI). Since the Marshallese people have an increased plasma content of an as yet poorly characterized iodoprotein, the PBI determinations gave a falsely high level of T_4, possibly masking hypothyroidism.[14] Hypothyroidism in subjects No. 3 and 5 (Table 3) was first suspected ten years after exposure, when these children showed growth retardation and delayed skeletal maturation. It was not until more specific methods for T_4 and TSH quantitation were used that the clinical diagnosis was confirmed by chemical measurements (Table 3). The TSH level was 500 μU/mL and the FT_4I was markedly depressed in a plasma sample from subject No. 5 obtained in 1963. Subject No. 3 was already receiving levothyroxine replacement at the time of the first sample (still available), but a thyroxine iodine (T_4I) of 0.8 μg/dL was found in 1965 (normal range, 3.0 to 6.4 μg/dL). Neither subject had had thyroid surgery. The results in Table 3 show that the plasma TSH level was unequivocally elevated in three other subjects (No. 2, 33, and 69). In these individuals, hypothyroidism was not apparent. In subject No. 69, the plasma FT_4I was markedly depressed, and it was low normal in subject No. 2. The reason for the apparent discrepancy between the FT_4I of 6.8 units and the serum TSH concentration of 22 μU/mL in subject No. 33 is unclear. Prophylactic levothyroxine treatment had already been begun in the Rongelap population in 1965, and this plasma sample was obtained in 1966. Since several weeks of thyroid therapy are required to suppress TSH to normal levels, a normal plasma FT_4I such as found in subject No. 33 in the presence of an elevated TSH level probably indicates that levothyroxine treatment had not been maintained regularly over the previous months. In two other persons (No. 19 and 83), plasma TSH concentrations were above the upper limits of normal, but no other samples were available to confirm these borderline elevations. The low (No. 19) or subnormal (No. 83) FT_4I is consistent with the diagnosis of modest thyroid dysfunction.

Results of Prospective Evaluations

Determinations of TSH levels have been performed on two or more occasions in plasma samples from 36 persons who were on Rongelap or Ailingnae during the fallout and who have not had thyroid surgery. Prophylactic levothyroxine administration had been discontinued at least two months previously. In six per-

sons, the plasma TSH level was 6 μU/mL or greater on two separate occasions (Table 4). In all, the plasma FT_4I was subnormal, though not extremely low. Four of the six were evaluated for thyroid gland reserve by administration of exogenous thyrotrophin, and all had a subnormal increment in plasma T_4. In five, protirelin infusion tests were performed. The plasma TSH level at 20 minutes was in excess of the upper limits of normal observed in euthyroid Marshallese in all consistent with the modest elevation in basal TSH levels. Before surgery for removal of a thyroid nodule in 1976, one other subject with a calculated thyroid dose of 425 rad had basal plasma TSH concentrations of 5.1 and 4.9 μU/mL, and the plasma TSH level after protirelin administration was 36 μU/mL at 20 minutes and 48 μU/mL at 40 minutes, suggesting early thyroid dysfunction. The increment in plasma T_4 concentration 24 hours after thyrotrophin administration was 0.8 μg/dL, and the FT_4I was 5.6 units.

Because most of the subjects in Table 4 were between the ages of 50 and 69 years, evaluation of plasma TSH levels in 53 unexposed Marshallese between the ages of 50 and 70 years was performed. In only one person, subject No. 982, mentioned previously, was the TSH level greater than or equal to 6 μU/mL. Ninety percent of the plasma TSH concentrations were less than 3 μU/mL in the older group, as in the entire Marshallese control population sample. Titers of antimicrosomal and antithyroglobulin antibodies were normal in plasma from exposed subjects.

COMMENT

The association of radiation exposure to the thyroid gland with the subsequent development of thyroid nodules is well recognized.[4,7,13] The appearance of hypothyroidism after accidental exposure to radioactive iodines contained in fallout has not been reported previously except in this Marshallese population. Studies by Rallison et al[14] did not show an increased number of cases of overt hypothyroidism in children exposed to low levels of fallout in Utah. Most previous studies of the effects of radioiodine on human thyroid function have consisted of evaluations of the risk of hypothyroidism developing after various quantities of sodium iodide I 131 administered deliberately for the treatment of hyperthyroidism.[7] Such treatment generally results in thyroidal doses in excess of 5,000 rad. Based on these studies, it has been estimated that four to five cases of primary hypothyroidism per 10^4 persons per rad per year would appear from thyroidal exposure to ^{131}I greater than 2,500 rad.[15,17]

The results presented in Tables 3 and 4 are of considerable interest in light of the aforementioned estimate. Nine of the subjects listed in Tables 3 and 4 who had moderate to severe thyroid hypofunction were all young at the time of radiation exposure and, therefore, received the highest dose of radiation as a consequence of the small size of the thyroid gland. The thyroid hypofunction in the older subjects with lower exposure (Table 4) was less pronounced, but the plasma TSH concentrations are consistently greater than those found in the control Marshallese population, and the FT_4I values are all reduced. Using the same TSH assay as employed in these studies, a plasma TSH level of 6 μU/mL maintained for six hours by protirelin infusion results in substantial thyroid gland stimulation in normal persons.[18] Further evidence of decreased thyroid reserve in the exposed Marshallese is the decreased response to thyrotrophin and enhanced protirelin responsiveness. These abnormal plasma TSH concentrations are not found in a comparably aged, euthyroid, unexposed population, indicating that this is not a manifestation of age alone. No individual in either group had elevated titers of antithyroid microsome or antithyroglobulin antibodies. The estimated dose to the thyroid in the subjects in Table 4 was about one third of that of the subjects listed in Table 3, with the exception of patient No. 32.

Virtually all of the persons found to have evidence of thyroid hypofunction were on Rongelap at the time of fallout exposure. None of the Utirik population and only one of those on Ailingnae (No. 16) was affected. If the risk of hypothyroidism associated with ^{131}I therapy for hyperthyroidism (four to five cases per 10^4 persons per rad per year) is used to calculate the expected number of hypothyroid subjects 25 years after exposure only in those 22 subjects who were younger than 10 years of age at the time of exposure (mean estimated thyroid dose, approximately 1,200 rad), only three such cases would be expected. The fact that seven subjects were already hypothyroid within 14 years of exposure indicates that the prevalence of this complication is considerably higher than predicted. In the surviving Rongelap and Ailingnae subjects who have not had thyroid surgery (n=36), only two cases of hypothyroidism would be expected, assuming an average dose of 400 rad. Five such persons were observed.

The major reason for this apparent discrepancy may derive from the type of radiation received by the Marshallese. Perhaps only one third of the thyroid dose in the Rongelap and Ailingnae subjects was due to ^{131}I, the remainder being derived from the shorter-lived isotopes ^{132}I, ^{133}I, and ^{135}I. There are reasonably good data to suggest that radiation from ^{131}I is only one fourth to one tenth as effective as an equivalent dose of x-irradiation in producing thyroid damage owing to the higher dose rate achieved with the latter.[19,20] However, the short-lived isotope ^{132}I is as effective in destroying thyroid tissue as is x-irradiation, and the same may be true of ^{133}I and ^{135}I.[19,20] Hence, the use of figures from data on thyroid radiation effects due to ^{131}I will give a considerably lower estimate for hypothyroidism than would be expected for the Marshallese subjects, owing to the significant contribution from short-lived, more biologically effective isotopes of iodine.

The following calculation shows the potential importance of the short-lived isotopes of iodine to the estimates of thyroidal dose. It is given as an example only and should not be used as a revised dose calculation for this population. If the total dose to the thyroid due to internal deposition of radioiodines were three times that due to ^{131}I and ^{132}I, ^{133}I and ^{135}I are assumed to be roughly seven times (range, four to ten times) more destructive per rad than ^{131}I,[19,20] a "^{131}I equivalent" dose to the thyroid can be derived. For example, a person receiving a total dose to the thyroid of 900 rad would sustain 300 rad from ^{131}I,

at approximately 4,200 rad (600 rad × 7) in ^{131}I equivalents from short-lived iodine isotopes. Such a "correction" could well make the high prevalence of hypothyroidism in the exposed Marshallese more in keeping with the expectations from the experience with therapeutic ^{131}I.

Several other factors may be contributing to the fact that the prevalence of hypothyroidism in this population is greater than is observed after ^{131}I exposure. The estimates of thyroid exposure, particularly that due to the short-lived isotopes of iodine, is only approximate for the reasons already discussed and could have been underestimated. A reevaluation of these calculations is currently under way at Brookhaven National Laboratory. Second, the hypothyroidism on which the risk estimates are based has largely been overt, whereas the present study has employed sensitive biochemical techniques not generally used in previous studies. A third consideration is that the early and severe thyroid dysfunction occurred in persons exposed as very young children, whereas the risk estimates are based almost exclusively on data obtained in adults with hyperthyroidism. The radiosensitivity of the young thyroid, at least for neoplastic changes, is greater than that in older persons.[8] Whatever the reason(s), it is apparent that, while the true prevalence of hypothyroidism is not definable in this population because of thyroid surgery in many of the patients at highest risk, it is considerable. From the results in Table 3, one must even consider the possibility that an elevation in the TSH level could have contributed to the development of the early thyroid nodularity. Such a possibility justifies the prophylactic administration of levothyroxine sodium in the exposed Rongelap and Ailingnae population.

The high frequency of delayed thyroid disease after a nuclear explosion over 100 miles distant is striking. Continued careful medical observation of the exposed Marshallese will be required for the possible development of hypothyroidism, as well as thyroid nodularity.

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