Reprinted from RADIATION-ASSOCIATED
THYROID CARCINOMA
Edited by Leslie J. De Groat, M.D., et. al.

SUMMARY OF THYROID FINDINGS IN MARSHALLESE 22 YEARS AFTER EXPOSURE TO RADIOACTIVE FALLOUT

Robert A. Conard, MD

Medical Department, Brookhaven National Laboratory
Upton, New York 11973

BACKGROUND

Inhabitants of several atolls in the Marshall Islands were accidently exposed to fallout radiation following a detonation of a high yield thermo-nuclear device during experiments at Bikini in the Pacific Proving Grounds in March 1954. An unpredicted shift in winds caused deposition of significant amounts of fallout on four inhabited atolls to the east of Bikini (see Fig. 1) and also on 23 Japanese fishermen aboard their fishing vessel, the Lucky Dragon. Sixty-four inhabitants of the island of Rongelap, 105 nautical miles away from the detonation, received the largest fallout exposure (an estimated dose of 175 rads of whole-body gamma radiation, contamination of the skin sufficient to result in beta burns, and internal absorption of radioactive materials through inhalation and ingestion). Another 18 Rongelap people, fishing on a nearby atoll (Ailingnae), where less fallout occurred, suffered lesser effects (receiving an external gamma dose of about 69 rads). There were 28 American servicemen on the island of Rongerik further to the east who received about the same exposure as did the Rongelap people on Ailingnae. Lastly, 157 Marshallese on Utirik Island, about 200 miles further east, received an estimated 14 rads of whole-body radiation. These islanders were all evacuated to the Naval Base at Kwajalein,to the south, by two days after the accident, where they received medical examinations for the following two months. The Utirik people showed few if any effects and were returned to their home island. The American servicemen, who showed only slight effects, were later returned to duty. The Rongelap people showed the greatest effects and lived temporarily on an island to

the south. In 1957 Rongelap was considered radiologically safe, and they were moved back to a new village. A group of more than 200 Rongelap people who were relatives of exposed people, but had been away from the island at the time of the accident, moved back with the exposed people to their home island and have served as an ideal comparison population for the studies. Medical examinations have been carried out on these populations for the past 22 years.

The most serious acute effects of the exposure were due to penetrating gamma radiation. These included transient anorexia, nausea and vomiting, and significant depression of the peripheral blood elements in many members of the higher exposure Rongelap group. The hematological depression (to about half normal level by six weeks) was not sufficient to produce definite clinical signs and required no specific therapy. Blood levels returned to near normal by one year. Contamination of the skin in the Rongelap group resulted in widespread beta burns and epilation. These lesions healed and hair regrew normally within several months.

Radiochemical urine analyses revealed that measurable amounts of radionuclides were absorbed internally from ingestion of contaminated food and water and from inhalation (see Table 1). It is noteworthy that no acute effects due to this internal exposure were seen, in view of the late thyroid effects from radioiodine absorption to be described below.

Followup examinations have revealed, except for one fatal case of leukemia and extensive thyroid lesions, only a few findings that might be related to radiation exposure, and space does not permit a discussion of these here[4]. The above findings have been reported in numerous publications (-5) and presented in detail in a twenty-year review (6).

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[4] In addition to annual examinations the people have been seen on a quarterly basis by our resident physicians in the islands, Drs. K. Knudsen and K. Kotrady.

THYROID DOSIMETRY

The fallout produced several possible sources of radiation exposure to the thyroid gland in addition to the gamma radiation. Iodine isotopes are produced in relatively high yields by the fission process. Some are too short-lived to be of consequence, but iodine 131, 132, 133, and 135 are sufficiently long-lived to have been present at the time the fallout cloud arrived at the inhabited atolls. Thyroid lesions were not expected, on the basis of earlier estimates of thyroid dose from internal absorption of radioiodines. In 1964 when thyroid nodules first began to appear, thyroid doses were re-evaluated by James (7). Calculations of the thyroid dosage from radioiodines unfortunately had to be based on the ^{131}I content of a single pooled urine sample from Rongelap people collected at 15 days post exposure. The shorter-lived isotopes of iodine delivered 2 to 3 times the estimated dose delivered by ^{131}I alone. The importance of these shorter-lived, more energetic isotopes must be kept in mind in assessing the dose-response relationship for thyroid effects. The dose to the thyroid of a Rongelap adult, including gamma dose, was calculated to be about 335 rads (220-450 rads) and to that of a 3-year-old Rongelap child as 700-1400 rads. The larger doses in the children were due mainly to the smaller sizes of their thyroids. The thyroid doses in the lesser exposed populations were extrapolated from those of the Rongelap group on the basis of the ratio of gamma doses. Individual children's doses were calculated by using a linear relationship between the estimated thyroid size and regression lines drawn for the three exposed populations.

EARLY THYROID EFFECTS

Beginning several years after exposure it was noted that 5 of 19 children exposed at < 10 years of age showed retardation of growth. Examinations during this early period did not reveal any recognizable thyroid abnormalities, and the protein bound iodine (PBI) levels in these children as well as in all Marshallese were in the normal to high normal range. Two boys

Table 1

ESTIMATED BODY BURDEN (μCi) OF RONGELAP PEOPLE

	Activity at day 1	Activity at day 82
^{89}Sr	1.6 - 2.2	0.19
^{140}Ba	0.34 - 2.7	0.021
Rare earth group	0 - 1.2	0.03
^{131}I (in thyroid gland)	6.4 -11.2	0.0
^{103}Ru	0 - 0.013	-
^{45}Ca	0 - 0.019	0.0
Fissile material	0 - 0.016 (μg)	0.0

became particularly stunted in growth (8). They had been exposed at one year of age, and they gradually developed atrophy of the thyroid gland and signs of myxedema.

In 1965 thyroxine analysis by ion exchange column showed that some of the children did indeed have low serum thyroxine levels. Control studies on normal Marshallese revealed that many of them had unusually high iodoprotein levels, which had led to a false interpretation of the PBI determination (9). It then became apparent that low thyroxine (T_4) levels in some of the children had probably been masked by high levels of iodoprotein.

THE DEVELOPMENT OF THYROID LESIONS

Evidence for retardation of growth related to thyroid injury was soon followed by discovery of a thyroid nodule in a 12-year-old girl in 1963, 9 years after

exposure. Subsequently there was continuing development of thyroid nodules in the Rongelap and Ailingnae populations and more recently in the least exposed Utirik population. At present 40 of 243 exposed Marshallese (16.5%) are affected (ratio of females to males affected is 2:1). Table 2 shows the numbers of benign and malignant tumors in the different groups with estimated average thyroid dose and comparison of those exposed at < 10 and > years of age. There appears to be a dose related response, with the greatest incidence of tumors in the Rongelap children (75%). Thyroid surgery has been performed on 31 exposed Marshallese and 3 unexposed[2]. The thyroid glands of most of the exposed Rongelap people undergoing surgery contained multiple nodules or areas of adenomatous change. Often those with only one palpable nodule proved to have multiple nodules. Microscopic examination showed that many of the lesions were surrounded by a capsule and, unlike the remainder of the gland, had distinct histological patterns ranging from microfollicular to fetal, solid, or embryonal types, and many showed hemorrhagic or degenerative changes (6). Adenomatous changes were not unlike those seen in chronic iodine deficiency, except that most of the goiters were smaller in the Marshallese. Many of the glands were found to contain minute lesions, some composed of solid cell masses, which, although considered benign, were composed of discrete areas of atypical cells suggestive of malignant potential. Seven cases of cancer of the gland have been found, all in females, 2 in the younger age group (see Table 3). These tumors were relatively well differentiated, 3 papillary, 1 follicular, and 3 mixed types. Two were 2-3 cm, 3 about 1 cm and 2 between .5 and 1 cm in size and all were the tumor of concern on palpation. Four had localized metastasis or blood vessel invasion. The latent periods varied between 11 and 22 years. Most of the women in whom cancer was diagnosed had multiple pregnancies prior to development of their tumors. More than 5 years has elapsed in five cases without evidence

[2] Thyroid surgery was done by Drs. B.M. Dobyns, Case Western Reserve U, B. Colcock, Lahey Clinic and L.C. Broadus, U.S. Navy.

Table 2
THYROID TUMORS IN MARSHALLESE (1976)

Cases/original number in group)

GROUP	CHILDREN (Age < 10 at exposure) Thyroid Dose Average	Total Tumors	%	Cancer	%	ADULT (Age > 10 at exposure) Thyroid Dose Average	Total Tumors	%	Cancer	%
Rongelap	1010	18/23	78	1/23	4.3	379	6/45	13	3/45	6.7
Ailingnae	382	2/6	33			135	4/12	33		
Utirik	83	1/58	1.7	1/58	1.7	30	9/99	9.1	2/99	2.0
All	317	21/87	24	2/87	2.3	139	19/156	12.2	5/144	3.5
Unexposed		3/199	1.6	1/199	0.5		20/313	6.4		

TABLE 3

THYROID CANCER CASES IN MARSHALLESE EXPOSED TO FALLOUT (as of September, 1976)

	Sex	Dose (rads)	Age Exposure	Ca	Years Latent	Type	Metastases	Other Thyroid Lesions	Surgery	Years Post-op
Rongelap										
#72	F	905	6	22	15	Papillary, one focus(?)	Multiple cervical nodes	Multiple adenomas	TT L-RND	7
#64	F	335	29	40	11	Mixed, one focus	1 node,Bl. vessel invasion	None	NTT 30 MCi ^{131}I	12
#18	F	335	21	36	15	Papillary, one focus	None	Multiple adenomas	TT	7
#74	F	425	16	38	22	Papillary	None	Multiple adenomas	L-L	<1
Utirik										
#2229	F	31	21	36	15	Follicular, Other foci	Bl. vessel invasion	Multiple adenomas	R-L	7
#2160	F	70	4	24	20	Mixed	None	None	L-L	<1
#2194	F	31	37	53	16	Mixed, one focus	Multiple lt. nodes	Multiple adenomas	TT	<1

Surgery = Subtotal (STT), near-total (NTT), total (TT), lobectomy (L), radical dissection (RND).

Table 4

THYROID TUMOR RISK vs. DOSE

(Cases/10^6/rad/yr)

	Children (Age < 10 at exposure)				Adults (Age > 10 at exposure)		
Group	Yrs Follow up	Thyroid Dose Average	Benign*	Ca.	Thyroid Dose Average	Benign*	Ca.
Rongelap		1010	33	2.4	379	16	6.4
Ailingnae	22	382	40		135	142	
Utirik		83		9.5	30	8	26.4
All		317	29	3.5	139	14	10.5
Rochester[16]	17	335	64	5.5			
Ann Arbor[16]	17	20	24	2.2			
UNSCEAR[17]	17	100 - 300		0.5 - 1.5			
ABCC[18]	20	20 - 1000		1.3 (all ages)			

*Corrected for control incidence

of progression of the disease. Three of the cases of thyroid cancer were in the Utirik group, two occurring in the past year. Though highly significant statistically, this is a puzzling development, since the number of benign tumors does not appear to be increased in this group, with none appearing in the high risk group of 58 children aged < 10 at exposure.

One of 4 Rongelap children exposed *in utero*, exposed at the end of the second trimester, (175 rads of gamma radiation and an unknown amount of radioiodine from the mother), developed benign thyroid nodules 20 years after exposure. Though a number of cases of myxedema have been reported in babies born of mothers treated with radioiodine, this is thought to be the first case of nodularity reported. Fig. 2 shows that at 22 weeks the thyroid is actively functioning in the fetus, though it is not possible to calculate the dose to the gland of this particular boy. It is noteworthy that his mother had a thyroid cancer removed during the past 6 months. The boy has not shown any other effects of his *in utero* exposure. The other 3 subjects exposed *in utero* have appeared to be normal.

LATENT PERIOD

Fig. 3, a plot of the time of development of thyroid tumors vs dose, indicates that thyroids that received lower doses developed tumors later than those receiving higher doses. This effect on latent period seems to be roughly dose dependent. Other studies of radiation induced cancers in people exposed as children have not demonstrated clear-cut correlation between radiation and length of latent period (11). However, most of these studies suffer from uncertainty of exact dosage and insufficient spread of doses and of times when thyroid tumors actually developed. Some degree of dependence of latent period on dose seems reasonable, since a higher dose causes greater cell destruction resulting in greater thyroid hypofunction and thyroid stimulating hormone (TSH), which is thought to be an important factor in neoplasia induction, as discussed earlier by Dr. Doniach. With lower doses more cells

may go through more cell divisions before succumbing to radiation effects, whereas with higher doses the cells may die at their first mitosis.

EFFECT OF THYROXINE TREATMENT

In 1965 a panel of thyroid specialists, after reviewing the findings, recommended that the heavily exposed Rongelap group be placed on replacement thyroxine for life in order to block TSH secretion by the pituitary. Synthetic L-thyroxine (Synthroid) has been used. Two years ago the Ailingnae and *in utero* exposed groups were also placed on this treatment. Those of the Utirik people who developed thyroid tumors are also being given thyroxine. It was hoped that this suppressive therapy would inhibit development of neoplasia, and that growth and development in the hormone-deficient children would be enhanced. It has been difficult to maintain a strictly regular treatment regimen, but the treatment has been of benefit in enhancing growth and development in the growth retarded children and in maintaining a normal metabolic state in the operated cases. Fig. 4 shows the improvement in growth and development in one of the stunted boys, shown standing beside his younger brother.

It is uncertain whether or not the treatment has had any effect in preventing the development of nodules in the exposed Rongelap people. Some tumors developed before therapy was instituted. Since then, however, 14 people in this group who were not always consistent in taking their medication, but some of them were thought to be conscientious about it. In two cases nodules appeared to diminish on therapy.

THYROID FUNCTION

Tests of thyroid function were carried out in the earlier years by PBI analyses, later by an improved method involving ion exchange and more recently, by radioimmunoassays for T_4, triiodothyronine (T_3), TSH, thyroxine binding globulin (TBG) and thyroglobulin (TG). Since 1974 function has also been tested by T_4 incre-

ment following exogenous TSH stimulation, and by endogenous TSH response to thyrotropin releasing hormone (TRH)[3]. It has not been feasible to do thyroid scans in the islands. The results indicated the following: 1) Prior to surgery some subjects with nodules had reduced T4 levels. 2) Following surgery nearly all patients, in spite of attempted thyroxine therapy, exhibited reduced function on occasion, which showed that the remaining tissues were not capable of maintaining a euthyroid state. 3) Recently about 50% of the exposed Rongelap people showed biochemical hypothyroidism without clinical evidence of thyroid disease, a finding that probably portends trouble ahead.

RISKS FOR RADIATION-INDUCED TUMORS IN THE MARSHALLESE

The data on the Rongelap people in Table 4 indicate that, on a risk per rad basis, the incidences of benign and malignant thyroid lesions are about the same for them as for groups exposed to x or gamma radiation, except for the higher risk values for the Utirik adults. Clinical experience suggested that ^{131}I is less effective than x-rays in producing thyroid tumors. This may in part be due to dose rate and the soft beta radiation of that isotope, much of which is wasted in the colloid of the larger follicles not reaching the follicular cells. The higher energy of the short-lived isotopes of iodine (particularly ^{132}I, ^{133}I, and ^{135}I), resulting in higher dose rate and more uniform exposure of the thyroid, is thought to have been the important factor in increasing the number of thyroid abnormalities above that expected from similar doses from ^{131}I alone (12-13). This reasoning is supported by a number of animal experiments (14-15).

[3] Thyroid uptake studies were done by Drs. J.E. Rall and J. Robbins at NIH, and by Dr. H.L. Atkins at BNL; RIA studies, by Dr. P.R. Larsen at Peter Bent Brigham Hospital and by Drs. J. Robbins, M. Gershengorn, M. Izumi, and J.L. Baulieu at NIH.

COMMENTS AND CONCLUSIONS

From the Marshallese experience it appears that the greater propensity for the development of thyroid nodularities after radioiodine exposure in the children than in the adults is related not only to the smaller size of their glands (resulting in larger doses) but possibly also to the rapid growth of the gland from 1-2 grams at birth to 18 at maturity. Other factors such as the stress of puberty and frequency of pregnancy may also have played a role.

The lower incidence of thyroid cancer in the Rongelapese exposed as children, than in those exposed as adults, is worthy of comment. One can postulate that the thyroid doses in the Rongelap children (700-1400 rads) were high enough to cause many cells to die at mitosis because of lethal damage to the reproductive mechanism and thus to reduce the number of cells at risk for malignant transformation. At lower doses, as in the adult group, a greater number of cells would be spared for malignant transformation. One would have to assume that in the children's thyroids the high dose effect overrode the possible enhancing effect of the growth factor for cancer induction. The high incidence of benign thyroid tumors in the children could be due to the increased cell destruction with greater hypofunction and increased TSH stimulation of the remaining cells producing many small nodules. With doses in a still higher range (> 2000 rads?) one might expect such extensive cell destruction to result in hypothyroidism and, because of the fewer surviving cells at risk, fewer tumors. This is the situation in patients developing hypothyroidism years after radioiodine treatment for Graves' disease. Perhaps the two Marshallese boys who developed myxedema without thyroid nodules received doses in this higher range.

It is quite likely that the final tally of thyroid tumors in the Marshallese is incomplete at this time since new lesions are still occurring. The mean latent period for radiation-induced thyroid tumors may be as long as 30 years (11). Furthermore, on the basis of

the present data the risk of developing radiation-induced thyroid neoplasia is probably underestimated, since surgical removal of potentially malignant tissues may have occurred and the hormone treatment may have inhibited the development of some tumors. Also, as pointed out above, the true carcinogenic potential of the exposure, particularly in the children receiving the higher dose, may have been masked by excessive cell destruction. The recent finding that subclinical thyroid deficiency is present in some of the exposed people who have not shown any thyroid abnormalities also indicates that the thyroid effects in the Marshallese may not yet be completely manifest, and continued careful surveillance of this population is necessary.

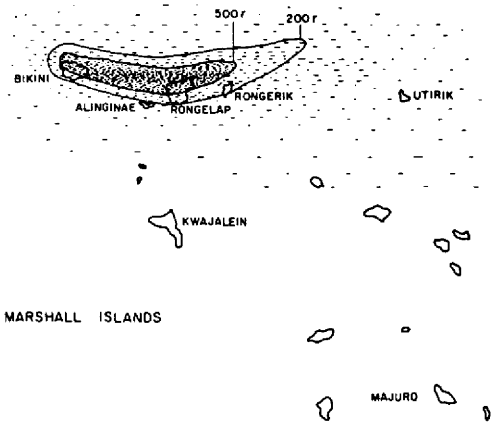

Fig. 1. Map of fallout area, Marshall Islands, March 1, 1954.

8-142-58

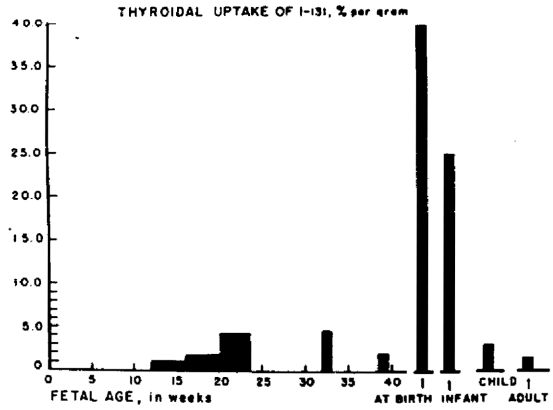

Fig. 2. Thyroidal uptake of ^{131}I (% per gram) versus age. From Evans et al. (10).

8-47-74

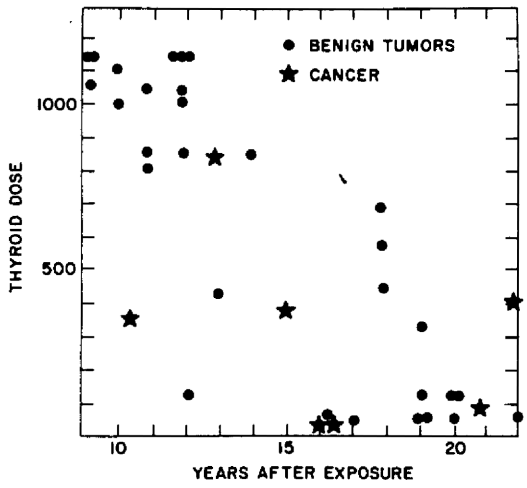

Fig. 3. Time of appearance of thyroid tumors related to dose.

9-1032-76

Fig. 4. Right: Subject No. 3 and his younger brother (No. 83) in 1963. Left: Same boys in 1973 after No. 3 had been given thyroid hormone for 8 years.

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