

The Medical Research Center  
Brookhaven National Laboratory  
Upton, L. L, New York

*File Copy*

#2157  
BNL#34496

401830

*Radiation Carcinogenesis: Epidemiology  
and Biological Significance, edited by  
J. D. Boice, Jr. and J. F. Fraumeni, Jr.  
Raven Press, New York 1984.*

REPOSITORY BNL RECORDS  
COLLECTION MARSHALL ISLANDS  
BOX No. MEDICAL DEPT. PUBLICATIONS  
FOLDER # 2099 - 2171

## Late Radiation Effects in Marshall Islanders Exposed to Fallout 28 Years Ago

Robert A. Conard

*Brookhaven National Laboratory, 32 Ivy Lane, Setauket, New York 11733*

In 1954, following detonation of a megaton nuclear device at Bikini, an unfortunate accident occurred owing to an unpredicted shift in winds resulting in exposure to radioactive fallout of 250 Marshallese people, 28 American servicemen on atolls to the east, and 23 Japanese fishermen on their fishing vessel. In this presentation, medical findings in the exposed Marshallese noted over the past 28 years will be briefly reviewed with particular emphasis on late effects on the thyroid gland. Details of the accident, evacuation of the people, and medical surveys and findings can be found elsewhere (10-14,37,55).

The exposure of the Marshallese differs from the exposure of the Japanese at Hiroshima and Nagasaki. The Japanese were exposed directly to the detonating bombs, and this resulted in gamma and neutron radiation, and blast and thermal trauma, with considerable early mortality. The Marshallese on the other hand were too far distant from the detonation for any direct effects, and their exposure was due entirely to fallout radiation during the 2 days prior to evacuation. This consisted of penetrating whole-body gamma radiation, irradiation of the skin (principally beta radiation) from fallout deposited on the skin, and internal absorption of radionuclides from ingestion of contaminated food and water. The most serious internal exposure was that to the thyroid from radioiodines, which were relatively abundant in the fallout.

### DOSIMETRY

Table 1 shows the estimated doses (whole body and thyroid) received by the Marshallese on the three atolls (at approximate distances from Bikini of 100 miles on Rongelap, 90 to 100 miles on Ailingnae, and 300 miles on Utirik).

It should be emphasized that these are only rough dose estimates, since many uncertainties were involved in the dose calculations (13,33). On the basis of the degree of hematological depressions in the different groups, the whole-body gamma dose estimates do not appear to be far out of line. There is much greater uncertainty regarding the thyroid doses, which is unfortunate because dose-effect relationships for these findings are of considerable interest. The thyroid

TABLE 1. *Estimated radiation doses in exposed populations*

Atoll	No. affected <sup>a</sup>	Est. whole-body gamma dose (rem)	Est. thyroid dose (rem) by age at exposure		
			< 10 yr	10–18 yr	> 18 yr
Rongelap	67	175	800–2,000(?)	334–810	335
Ailingnae	19	69	275–450	190	135
Utiirik	164	14	60–95	30–60	30

<sup>a</sup> Includes in utero exposures (3 on Rongelap, 1 on Ailingnae, and 6 on Utiirik).

doses were due to gamma radiation plus radioiodines.<sup>1</sup> Because of the smaller size of the thyroid gland in children, their exposure from radioiodines was considerably greater. Although the estimated dose in a 3-year-old Rongelap child was 700 to 1,400 rads, the dose to a 1-year-old child was perhaps 2,000 or more rads. These dose estimates unfortunately had to be based on a single pooled 24-hr urine sample from Rongelap people collected 15 days after exposure, with the assumption that the I-131 excreted in this sample represented 0.1% of the I-131 initially taken in (33). The short-lived radioiodines (I-132, I-133, I-135) were not measurable but were estimated to have contributed 2–3 times the dose from I-131 to the thyroid. The possible importance of these isotopes will be referred to later. The thyroid doses to the Ailingnae and Utiirik groups were arrived at by extrapolation based on relative gamma dose estimates.

### COMPARISON POPULATIONS

About 200 Rongelap people who were not on Rongelap at the time of the accident, matched as nearly as possible with the exposed group with respect to age and sex, have been examined regularly for comparison purposes. In addition, during the past decade, about 400 other unexposed Rongelap people in the same age range as the exposed people and about 500 younger Marshallese have had thyroid examinations in order to establish the prevalence of thyroid abnormalities in unexposed Marshallese people. Though some of these "controls" have been exposed to slight residual radiation while living parttime on Rongelap and Utiirik, any effects of such low levels of exposure would not be detectable and would not nullify their use for comparative purposes (13).

### FINDINGS DURING THE FIRST DECADE

The early findings in the exposed Rongelap and Ailingnae groups (14) included transient nausea and vomiting, and depression of peripheral blood elements to

<sup>1</sup> Reevaluation of early dosimetry, now under way at Brookhaven National Laboratory with additional data that have become available, indicates that thyroid doses may be higher than previously estimated (39). In this report the earlier estimates shown in Table 1 are used.

about half normal levels, but without definite clinical signs or mortality and requiring no specific therapy. Contamination of the skin resulted in widespread "beta burns" and epilation. These lesions healed and hair regrew normally within several months. These findings were not seen in people exposed on Utirik and were present in the servicemen to a lesser extent. It is noteworthy that no early effects of the internal absorption of radioiodines or other radionuclides were noted. Indeed, nearly a decade passed before effects of thyroid exposure could be documented.

During the subsequent years, prior to the development of thyroid abnormalities, there were few findings that could be related to radiation effects (10-13). The general health of the exposed people appeared to be about the same as that of the unexposed people. Vital statistics suggested that mortality and fertility rates were about the same. During the first 4 years, there appeared to be an increase in miscarriages and stillbirths in the exposed Rongelap women, but this observation was uncertain in view of the small numbers involved. Genetic studies and examinations of the newborn have not revealed any detectable abnormalities that might be related to radiation exposure. A slight increase in chromosomal aberrations in lymphocytes was noted in the exposed Rongelap people. Neoplasia (including a fatal leukemia) and thyroid abnormalities are discussed below.

#### NEOPLASIA (NONTHYROID)

A number of benign tumors have been detected in both exposed and unexposed people in the normal range of expectancy (13).

It is noteworthy that in spite of widespread beta burns of the skin, no chronic radiation dermatitis or skin cancers have appeared, and only a minimum amount of scarring and pigmentation can be seen. A number of benign nevi were seen in the healed areas of neck lesions in several women, but these have not increased in recent years.

Two cases of pituitary adenomas have occurred. One was a nonfunctioning adenoma in a 40-year-old exposed Rongelap woman that developed several years after removal of a thyroid carcinoma. The patient responded well to x-ray therapy. The second adenoma was a prolactin-secreting tumor recently discovered in a 27-year-old exposed Utirik woman who is now undergoing treatment. In neither case was there evidence that hypothyroidism was a promoting factor, as has been reported (38,58). Neither does it seem likely that radiation exposure was the etiological agent, since pituitary adenomas have not been reported in recent reviews to be radiation induced (52).

Except for thyroid carcinomas, the documentation of possible radiation-associated malignancies in the Marshallese has been subject to uncertainties owing to the infrequency of autopsies or reporting of final diagnoses and unsatisfactory statistics on malignancies in the Marshallese people. A number of deaths in older women were thought to be due to cancer of the female genital tract,

which is not reported to be radiation induced in the exposed Japanese people (5). One death from cancer of the stomach in a Rongelap man exposed to 175 rads gamma radiation may have been related to his exposure.

Acute myelogenous leukemia developed in a 19-year-old Rongelap male who was exposed to 175 rads of gamma radiation at 1 year of age (12) and had a subtotal thyroidectomy for removal of benign nodules at age 13. He was treated for leukemia at the National Cancer Institute but responded poorly and died 6 months later. Retrospective studies of his hemograms indicated that he had had a relative neutropenia compared with other exposed and unexposed peers over a number of years prior to his death.

### THYROID ABNORMALITIES

It has been clearly demonstrated that the most widespread late effects of fallout exposure in the Marshallese have been related to radiation injury to the thyroid gland. With the development of thyroid hypofunction and benign and malignant nodules in the Rongelap population in the 2nd decade after exposure, extensive thyroid studies by thyroid experts have been carried out in both exposed and unexposed Marshallese.<sup>2</sup>

#### Hypofunction

A number of tests of thyroid function have been carried out by methods previously published (35,36). Serum samples have been analyzed for thyroxine ( $T_4$ ), thyroxine-binding globulin index (TBGI), triiodothyronine ( $T_3$ ), and thyroid stimulating hormone (TSH). Stimulation tests with thyrotropin-releasing hormone and TSH and tests for iodine uptake, scans, etc., were done on patients hospitalized for surgery. In view of improved radioimmunoassay and other techniques, retrospective analyses were done on stored frozen serum samples taken in earlier years.

The first indication of functional impairment of the thyroid was the observation, toward the end of the 1st decade, of growth retardation in some of the exposed Rongelap children. Numerous data have been collected on statural growth and osseous maturation in the exposed and control children over the years (13,54,55). In 1964 it was noted that two boys exposed at 1 year of age were stunted in growth and became myxedematous, and a number of other children exposed at less than 10 years of age had a slight degree of growth retardation. This was particularly true of the Rongelap boys exposed at less

<sup>2</sup>Some of the physicians who have been more actively involved in the thyroid examinations include Drs. D. E. Paglia (UCLA); B. Dobyns (Cleveland Metropolitan General Hospital, Cleveland); B. R. Larsen (Peter Bent Brigham Hospital, Boston); W. W. Sutow (deceased) (M. D. Anderson Hospital, Houston); J. E. Rall, J. Robbins, and J. Wolff (NIH, Bethesda); J. T. Nicoloff (University of Southern California, Los Angeles); B. Colcock (Lahey Clinic, Boston); W. Adams, H. Pratt, and K. Knudsen (Brookhaven National Laboratory); C. S. Hill, Jr. (M. D. Anderson Hospital, Houston); and D. D. Becker (Cornell Medical Center, New York).

than 5 years of age. Retrospective analyses of the frozen serum samples revealed that many of the children, prior to thyroid surgery, had elevated TSH levels and in some cases reduced  $T_4$  levels, though except for the two myxedematous boys, the hypofunction was not severe enough to be clinically evident.

In 1965  $T_4$  (synthroid) treatment was instituted in exposed Rongelap and Ailingnae populations with the objectives of retarding thyroid nodule formation and enhancing growth and development in growth-retarded children. It was given to surgical cases only in the Utirik and control populations. Results of this treatment will be discussed below.

In view of the early hypofunction of the thyroid noted in the children, the groups tested for hypofunction have included, in addition to the exposed Rongelap-Ailingnae groups, the exposed Utirik people and many unexposed people. On the basis of control studies in the unexposed Marshallese, an increase in TSH level to  $\geq 6 \mu\text{U/ml}$  on at least two occasions was considered positive evidence of hypofunction and levels between 3 and  $6 \mu\text{U/ml}$  were considered suggestive evidence. In some of the exposed children, the evaluation was based on only one available presurgical sample (13,37). These are very sensitive criteria and represent subclinical or "biochemical" hypofunction. In addition to TSH analyses, results of stimulation tests with TSH and TRH were used in many cases to confirm the findings. Table 2 summarizes these findings.

The most marked TSH elevations were noted in the Rongelap people exposed at less than 10 years of age, who had received the highest thyroid doses. Only two of these had clinical hypothyroidism, and most of the others subsequently

TABLE 2. Thyroid hypofunction (1981)<sup>a</sup>

Group age 1954	Est. dose (rads)	No.	Hypofunction			
			Positive		Positive + Sug- gestive	
			No.	%	No.	%
Rongelap						
1 yr	$\geq 1500(?)$	6	5	83	5	83
2-10	800-1500	16	4	25	8	50
$\geq 10$	335-800	45	4	9	6	13
Ailingnae						
< 10	275-450	7	0	0	0	0
$\geq 10$	135-190	12	1	8	2	17
Utirik						
< 10	60-95	64	0	0	4	6
$\geq 10$	30-60	100	1	1	4	4
Controls						
< 10		229	1	0.4	2	0.8
$\geq 10$		371	1	0.3	2	0.5

<sup>a</sup> The levels in the exposed groups have not been corrected for control levels, since the correction would be small. Includes presurgical data.

had surgery for removal of thyroid nodules. More recently a number of surviving adults, who received considerably less exposure, without detectable thyroid abnormalities, have shown modest increases in TSH levels. Since many in this group were over 50 years of age, tests of thyroid function were done in older unexposed people, and the results indicated that this finding was not due to age alone (37).

### Thyroid Nodules

In 1964 benign thyroid nodules were removed from three teenage Rongelap girls in the exposed group. Since then benign and malignant nodules have developed in the exposed Rongelap and Ailingnae groups, and more recently to a lesser extent in the exposed Utirik group. A number of such nodules have been noted in the unexposed comparison populations. Table 3 summarizes these findings. The six children exposed at 1 year of age, who had the highest doses, are compared with other children less than 10 years old and with people more than 10 years old at exposure.

A total of 46 exposed Marshallese (29 in the Rongelap-Ailingnae group and 17 in the Utirik group) have developed thyroid nodules, and 42 of these have had them removed. Of 600 people in the age-matched unexposed population, 35 had nodules and 14 have had surgery. Table 3 shows the greater development of thyroid nodules in the higher-dose Rongelap-Ailingnae group than in the lower-dose Utirik or matched control group. The greater prevalence in the younger members of the Rongelap group with the larger doses is in contrast to

TABLE 3. *Thyroid nodules (1981)<sup>a</sup>*

Group age 1954	No.	Est. thyroid dose (rads)	Total nodules		Carcinoma	
			No.	%	No.	%
Rongelap						
1 yr	6	≥ 1,500(?)	4	66.7	0	0
2-10	16	800-1500	13	81.2	1	6.2
≥ 10	45	387	6	13.3	3	6.6
Ailingnae						
< 10	7	275-450	2	28.6	0	0
≥ 10	12	140	4	33.3	0	0
Utirik						
< 10	64	60-90	5	7.8	1	1.6
≥ 10	100	53	12	12.0	2	2.0
Matched controls						
< 10	229		6	2.6	2	0.9
≥ 10	371		29	7.8	3	0.8

<sup>a</sup> Prevalence has not been corrected for control levels. The carcinoma prevalence is probably low, since all unoperated nodule cases were considered benign for this table. Occult carcinomas were not included as carcinomas.

the greater prevalence in the older ones among the unexposed people. The usual predominance of nodules in females was observed. Noteworthy was the development of benign nodules in two of three Rongelap men exposed in utero. In one, exposed at 22 weeks gestation, the thyroid was probably sufficiently functional to incriminate radioiodine transferred from the mother. In the other case, however, exposed at about 12 weeks gestation, the thyroid was probably not functional and perhaps the gamma exposure may have been responsible.

Histopathologic diagnoses of Marshallese thyroid lesions have been furnished over the years by a number of pathologists.<sup>3</sup> These are summarized in Table 4.

Most of the benign nodules were "adenomatous nodules," that is, did not fulfill the criteria of true neoplasms (44). These nodules were frequently multiple. The carcinomas were all of the papillary type, which are considered to behave in a clinically more benign fashion than follicular carcinoma or more undifferentiated types (1,23,45). The occult papillary carcinomas ("occult sclerosing carcinoma") (28,35) were found in association with adenomatous nodules. They were not listed in the malignant category in view of their generally recognized benign nature (21,23,27,51,61). No specific type of histologic lesion was noted in the exposed people, though histologic and cytologic changes associated with radiation injury, such as interstitial fibrosis, lymphocytic thyroiditis, and oxyphylic changes (25,53) were observed in some of the exposed individuals.

TABLE 4. *Histopathologic diagnoses of thyroid nodules (up to 1982)*

	Exposed group	Unexposed <sup>a</sup> group
No. in population	250	1303
No. with surgery	45	18
Diagnosis <sup>b</sup>		
Adenomatous nodule(s)	33	9
Adenoma	5	3
Atypical adenoma or adenomatous nodule	2	2
Occult papillary carcinoma	2	1
Papillary carcinoma	7	5
No diagnostic lesion	3	1

<sup>a</sup> Includes unmatched younger Marshallese.

<sup>b</sup> Includes more than one diagnosis in some cases.

<sup>3</sup> The pathologists that have contributed include Drs. S. Warren (deceased), W. A. Meissner, and M. Legg (New England Deaconess Hospital, Boston); D. E. Paglia (UCLA); J. D. Reid and M. Petrelli (Cleveland Metropolitan General Hospital); J. Oertel (Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D.C.); L. B. Woolner (Mayo Clinic, Rochester, MN); A. L. Vickery (Massachusetts General Hospital, Boston); L. V. Ackerman (S.U.N.Y. Stony Brook); W. Hawk (Cleveland Clinic, Cleveland); and D. Slatkin (Brookhaven National Laboratory).

Since most of the carcinomas in the Marshallese were in the younger age group and were of the papillary type without distant metastasis, the clinical prognosis for these individuals is excellent (8,26,61).

#### EFFECTIVENESS OF T<sub>4</sub> TREATMENT

Evaluation of the prophylactic effectiveness of T<sub>4</sub> treatment in preventing development of thyroid nodules has been complicated by difficulties in maintaining a strict treatment regimen. Lack of compliance with the regimen has been reflected in some cases in elevated TSH levels, particularly in postsurgical cases, where the hormone replacement is essential to maintaining a euthyroid state. Three patients who had benign nodules removed have had recurrence of nodules. All three of these exhibited elevated TSH levels prior to recurrence, indicating inadequate compliance with treatment.

The occurrence of thyroid nodules in the Rongelap-Ailingnae group appears to be slowing in the past few years (13), but this may be due to the smaller number of unaffected people living. (If one includes suggestive hypofunction, only 15 of 65 in this group now living have negative findings; in the Utirik group 93 of 115 now living have negative findings.)

Treatment with T<sub>4</sub> has undoubtedly been effective in enhancing growth and development in growth-retarded Rongelap children. A "catch-up" in growth has been sufficient that at maturity their statures were not statistically different from those of their unexposed peers (55).

#### DOSE-EFFECT RELATIONSHIPS

The increase in thyroid abnormalities in the exposed Marshallese people is undoubtedly related to radiation exposure. There are no known goitrogens that might play a role, iodine intake is adequate in the Marshallese, and the increase in thyroid abnormalities was roughly correlated with estimated radiation doses to the thyroid.

The association between radiation exposure and development of thyroid neoplasia has been well documented in animal studies (40-42), in children following therapeutic irradiation of the head and neck region (2,15,16,22,25,29,30,43,45,50), and in survivors of the atomic bomb exposures to gamma and neutron radiation in Japan (5,47,60). Reports of neoplasia following I-131 therapy are more limited (4,18), and it is generally conceded that such therapy is less tumorigenic than x radiation (6,48,56). The few studies looking for thyroid abnormalities following diagnostic use of I-131 have had generally negative results, though many people have probably had thyroid exposure of several hundred rads from repeated procedures (24,31,32). Some people living in Nevada and Utah near the nuclear test site were exposed to some fallout in the early 1950s. Thyroid dose estimates range from 18 to 120 rads or more (49). (The variability is due



to uncertainty regarding amounts of contaminated milk consumption.) It is not known if short-lived isotopes of iodine were involved. Thyroid examination of children from that area by thyroid experts 12 to 17 years later failed to reveal any increase in abnormalities of the gland (49).

Calculation of risks (cases/ $10^6$  persons/rad/year) for benign and malignant thyroid nodules, based on present estimates of the doses to the Marshallese, gave results in the same range as the risks reported for x radiation (3,6,30,56,60). The risk calculated for thyroid hypofunction was considerably higher than that reported following I-131 therapy (4,18). In interpreting these findings one has to keep in mind the uncertainty in the dose to the Marshallese. Preliminary results of reevaluation of thyroid doses at this laboratory indicate that the present estimates may be too low (39). If so, this would lower the risk estimates. However, one could not account for the findings on the basis of gamma or I-131 exposures alone. A large component of the thyroid dose in the Rongelap children was from radioiodines. The short-lived isotopes (I-132, I-133, I-135) are believed to have contributed two to three times the dose from I-131. A limited number of animal studies comparing the effectiveness of I-131 with that of x radiation (3,48,56,57) and of short-lived iodine isotopes (6,7,20,34,59,62) indicate that I-131 is less effective in producing thyroid abnormalities. The greater effectiveness of the short-lived isotopes seems to be related to more energetic beta rays and higher dose rate. It is unfortunate that more definitive studies of this type are not available, particularly with smaller doses of radioiodines. Even so, on the basis of available data, the possible importance of the short-lived radioiodines in the Marshallese exposure must be considered.

It should be pointed out with regard to the risk associated with thyroid hypofunction that sensitive biochemical techniques, not generally used, were employed in the Marshallese. Also, the more severe degrees of hypofunction were noted in the children, whereas most risk estimates for hypothyroidism are based on overt cases almost exclusively in adults treated for hyperthyroidism.

Doniach (19) has postulated a multistage development of radiation-induced thyroid neoplasia with radiation as the initiating factor and with secondary or promoting factors comprising mainly TSH stimulation secondary to glandular hypofunction and including increased growth rate and metabolism of the thyroid in children and possibly stresses of puberty and pregnancy. In addition to the increased doses in the children due to smaller glands, these promoting factors probably played a role. It was noted that most of the women who developed thyroid carcinoma had multiple pregnancies in the years prior to detection of their malignancy.

Even though the thyroid dose estimates in the Marshallese are uncertain and the number of cases is small, there are certain dose-effect relationships that seem likely. In Fig. 1 the percent occurrence of thyroid abnormalities is plotted according to dose range for the different groups (regardless of age). The data for the six Rongelap children exposed at 1 year of age are plotted separately, since they probably received doses that could be as high as 2,000

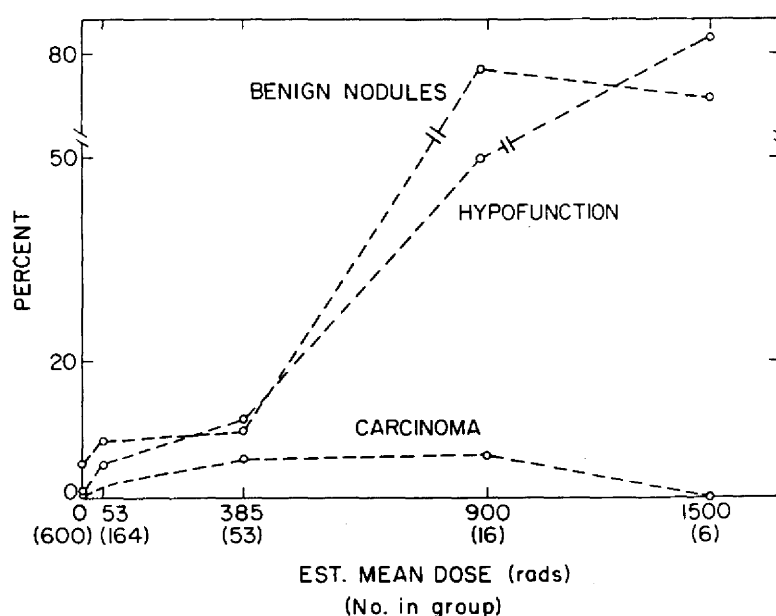


FIG. 1. Percent of persons with thyroid abnormalities (benign nodules, carcinomas, and hypofunction) in dose groups. All unoperated cases were considered benign for this calculation; therefore, the carcinoma incidence may be somewhat underestimated. Hypofunction includes both positive and suggestive cases. See text for composition of exposure groups.

rads or more.<sup>4</sup> The 900-rad group represents the Rongelap children exposed at 2 to 9 years of age, the 385-rad group are Rongelap adults and Ailingnae children, and the 53-rad group are the Utrik people (adults and children).

A few tentative interpretations might be drawn from the results in Fig. 1. Thyroid hypofunction appears to be a promoting factor for benign nodule development, since it roughly parallels the increase in nodularity at least in the 900-rad range. Perhaps such influence is reduced in the higher-dose group because of the "overkill" effect. This interpretation would be in keeping with the high incidence of hypothyroidism, but with few thyroid tumors, following large doses of radiation for treatment of hyperthyroidism (17,18). A low correlation of carcinoma with hypofunction suggests that hypofunction plays less of a promoting role for malignant transformation or that a plateau is reached at certain doses for such transformation. A plateau effect and reduced incidence of cancer have been noted with other types of radiation-induced neoplasms in

<sup>4</sup> It is noteworthy that of these six children five showed evidence of thyroid hypofunction with growth retardation, two of whom were myxedematous with markedly stunted growth but without thyroid nodules; four had thyroid nodules removed, of whom one has had a recurrence and another later died of acute myelogenous leukemia several years after thyroid surgery.

animals. The lack of carcinoma in the high-exposure group might therefore be due to an overkill effect.

The latent period before detection of hypofunction in the more highly exposed Rongelap children was shorter, and the hypofunction was more pronounced, than in the people receiving less exposure. Earlier cell death at mitosis in their growing thyroids and increased interphase death with these higher doses may have accounted for this. The later appearance of decreased thyroid function in the lower-dose adult group suggests that the delay was related to slower turnover of cells in the adult gland and probably to reduced interphase death at lower doses. Earlier appearance of nodularity in the younger age group would seem logically to be associated with earlier increased stimulation from TSH associated with the earlier hypofunction.

### DISCUSSION

The fallout accident involving the Marshall Islanders did not result in early mortality and, except for a case of leukemia and possibly one other cancer, late effects thus far have been predominantly thyroid abnormalities from exposure to internally absorbed radioiodines and gamma radiation.

Thyroid effects of the Marshall Islands accident are not strictly comparable with such effects that might occur from accidents involving nuclear power sources. Analysis of the Three Mile Island accident (63) has indicated that the amount of radioiodines released into the atmosphere was substantially less than that predicted in the *Reactor Safety Study* [the so-called Rasmussen Report (57)]. This should be kept in mind when comparing potential casualties from nuclear warfare versus reactor accidents.

In the event of nuclear warfare the total exposures from released radionuclides could be much larger than they were in the Marshall Islands accident. In such situations the effects of gamma radiation would likely predominate with regard to both early and late effects of exposure. Malignancies that might develop as a result of such exposure are more likely to be fatal than thyroid malignancies, which are more amenable to medical and surgical treatment.

From the Marshallese experience it is clear that, in any future accident involving radioiodines, the use of oral stable iodine to suppress radioiodine uptake by the thyroid, particularly in children and pregnant women, should be considered (9,46).

People who have been exposed to significant fallout should have regular examinations, including testing of their thyroid status with sensitive tests of thyroid function now available. Even though the prophylactic value of thyroid hormone treatment in preventing development of thyroid abnormalities has not been proved in the Marshallese or other humans, such treatment is sound and should be considered.

From the Marshallese experience it is apparent that more information is needed in several areas regarding their exposure.

1. More definitive studies are needed on the comparative effectiveness of I-131, short-lived iodine isotopes, and x rays in producing thyroid abnormalities. These studies should be done with large animals having thyroids nearer the size of human glands.

2. More data are needed on low-dose effects of x rays and radioiodines on the thyroid, including more data on effects from diagnostic use of I-131 and other radioisotopes.

3. Further information is desirable on other possible radionuclides that might be concentrated in the thyroid from fallout.

4. In view of the preponderance of thyroid abnormalities in the Marshallese children and in two exposed in utero, further data would be desirable on thyroid weight and function in children and human fetuses.

It is obvious that regular examinations of the exposed Marshallese must continue throughout their lifetime.

### ACKNOWLEDGMENTS

In addition to those people cited in the footnotes, many others, too numerous to mention here, have contributed to or participated in the examinations of the Marshallese over the past 28 years. Only a few of the organizations and people that have been so essential to the program can be listed here. Among these are Brookhaven National Laboratory (Drs. E. P. Cronkite, V. P. Bond, W. Adams, present director of the Marshallese studies, K. Knudsen, H. Pratt, D. C. Borg, and R. B. Aronson; and Messrs. W. Scott and P. Heotis, Ms. M. Dienes, and many others); the Department of Energy (Washington, Nevada, and Pacific Area Offices); the Department of the Interior, Government of the Trust Territory of the Pacific Islands, Government of the Marshall Islands and the Kwajalin Missile Range in the Marshall Islands; and the Marshallese practitioners and technicians. Most of all, we are grateful to the people of the Marshall Islands, the subjects of these examinations, for their cooperation and friendship over the years.

### REFERENCES

1. Ackerman, L. V., and Rosai, J. (1974): *Surgical Pathology*, pp. 316-319, C. V. Mosby, St. Louis.
2. Albert, R. E., and Omran, A. R. (1968): Follow-up study of patients treated by x-ray epilation for tinea capitis. *Arch. Environ. Health*, 17:899-918.
3. Beach, S. A., and Dolphin, G. W. (1962): A study of the relationship between x-ray dose delivered to the thyroids of children and the subsequent development of malignant tumors. *Phys. Med. Biol.* 6:583-598.
4. Becker, D. V., McConahey, W. M., Dobyns, B. M., Tompkins, E., Sheline, G. E., and Workman, J. B. (1971): The results of the thyrotoxicosis therapy follow-up study. In: *Further Advances in Thyroid Research, Vol. 1*, edited by K. Fellinger and R. Hofer, pp. 603-609. Gistel, Vienna.
5. Beebe, G. W., Kato, H., and Land, C. E. (1978): Studies of the mortality of A-bomb survivors.
6. Mortality and radiation dose. 1950-1975. *Radiat. Res.*, 75:138-201.

6. Book, S. A., and Bustad, L. K. (1973): Effects of radioiodine and x-ray on beagle pups. In: *Annual Report, 1973, Radiobiology Laboratory*, pp. 137-139. UCD 472-120.
7. Book, S. A., McNeill, D. A., Parks, N. J., and Spangler, W. L. (1980): Comparative effects of iodine-132 and iodine-131 in rat thyroid glands. *Radiat. Res.*, 81:246-253.
8. Cady, B., Sedgwick, C. E., Meissner, W. A., Bookwalter, J. R., Romagosa, V., and Werber, J. (1976): Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann. Surg.*, 184:541-543.
9. Cole, R. (1972): *Inhalation of Radioiodine From Fallout: Hazards and Countermeasures*. Defense Civil Preparedness Agency, Environmental Science Associates, Burlingame, California.
10. Conard, R. A. (1977): Summary of thyroid findings in Marshallese 22 years after exposure to radioactive fallout. In: *Radiation-Associated Thyroid Carcinoma*, edited by L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. Refetoff, pp. 241-257. Grune & Stratton, New York.
11. Conard, R. A. (1980): The 1954 Bikini Atoll incident: An update on the findings in the Marshallese People. In: *The Medical Basis for Radiation Accident Preparedness*, edited by K. F. Hubner and S. Fry, pp. 55-58. Elsevier/North Holland, Amsterdam.
12. Conard, R. A., Knudsen, K. D., Dobyns, B. M., Larson, R. P., Sutow, W. W., Rall, J. E., Wolff, J., Lowrey, A., and Cohn, S. H. (1975): *A Twenty-Year Review of Medical Findings in a Marshallese Population Accidentally Exposed to Radioactive Fallout*. Brookhaven National Laboratory Report BNL 50424. National Technical Information Service, Springfield, Virginia.
13. Conard, R. A., Paglia, D. E., Larsen, P. R., Sutow, W. W., Dobyns, B. M., Robbins, J., Krotosky, W. A., Field, J. B., Rall, J. E., and Wolff, J. (1980): *Review of medical findings in a Marshallese population twenty-six years after accidental exposure to radioactive fallout*. Brookhaven National Laboratory Report BNL 51261. National Technical Information Service, Springfield, Virginia.
14. Cronkite, E. P., Bond, V. P., Conard, R. A., Dunham, C. L., Farr, R. S., Shulman, N. R., Sondhaus, C. A., Cohn, S. H., Hechter, H. H., Sharp, R., Alpen, E. L., Browning, L. E., Wood, D. A., Rinehart, R. W., Cong, J. K., Robertson, J. S., and Milne, W. L. (1956): *Some Effects of Ionizing Radiation on Human Beings: A Report on the Marshallese and Americans Accidentally Exposed to Radiation Fallout and a Discussion of Radiation Injury in the Human Being*. U.S. Atomic Energy Commission Publication AEC-TID 5385. U.S. Government Printing Office, Washington, D.C.
15. Dolphin, G. W. (1968): The risk of thyroid cancers following irradiation. *Health Phys.*, 15:219-228.
16. DeGroot, L. J., Frohman, L. A., Kaplan, E. L., and Refetoff, S. R., editors (1977): *Radiation-Associated Thyroid Carcinoma*. Grune & Stratton, New York.
17. DeLawter, D. S., and Winship, T. (1963): Follow-up study of adults treated with roentgen rays for thyroid disease. *Cancer*, 16:1028-1031.
18. Dobyns, B. M. (1977): Radiation hazard—Experience with therapeutic and diagnostic <sup>131</sup>I. In: *Radiation-Associated Thyroid Carcinoma*, edited by L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. Refetoff, pp. 459-483. Grune & Stratton, New York.
19. Doniach, I. (1974): Effects of radiation on thyroid function and structure. In: *Handbook of Physiology, Sect. 7: Endocrinology; III: Thyroid*, edited by H. I. Greer and D. H. Soloman, pp. 359-375. Williams & Wilkins, Baltimore.
20. Dunning, G. (1956): Two ways to estimate thyroid dose from radioiodine in fallout. *Nucleonics*, 14:38-41.
21. Edis, A. J. (1977): Natural history of occult thyroid carcinoma. In: *Radiation-Associated Thyroid Carcinoma*, edited by L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. Refetoff, pp. 155-160. Grune & Stratton, New York.
22. Favus, M. J., Schneider, A. B., Stachura, M. E., Arnold, J. E., Ryo, U. Y., Pinsky, S. M., Colman, M., Arnold, M. J., and Frohman, L. A. (1976): Thyroid cancer occurring as a late consequence of head-and-neck irradiation: Evaluation of 1056 patients. *N. Engl. J. Med.*, 294:1019-1025.
23. Franssila, K. O. (1975): Prognosis in thyroid carcinoma. *Cancer*, 36:1138-1146.
24. Glennon, J. A., Gordon, E. S., and Sawin, C. T. (1972): Hypothyroidism after low dose <sup>131</sup>I treatment of hyperthyroidism. *Ann. Intern. Med.*, 76:721-723.
25. Greenspan, G. S. (1977): Radiation exposure and thyroid cancer. *J.A.M.A.*, 237:2089-2091.
26. Halnan, K. E. (1966): Influence of age and sex on incidence and prognosis of thyroid cancer: 344 cases followed for ten years. *Cancer*, 19:1534-1536.

27. Hazard, J. B. (1960): Small papillary carcinoma of the thyroid: A study with special reference to so-called nonencapsulated sclerosing tumor. *Lab. Invest.*, 9:86-97.
28. Hedinger, C., and Sobin, L. H. (1974): *Histological Typing of Thyroid Tumours*. World Health Organization, Geneva.
29. Hempelmann, L. H. (1968): Risk of thyroid neoplasms after irradiation in childhood. *Science*, 160:159-163.
30. Hempelmann, L. H. (1977): Thyroid neoplasms following irradiation in infancy. In: *Radiation-Associated Thyroid Carcinoma*, edited by L. J. DeGroot, L. A. Frohman, E. L. Kaplan, S. Refetoff, pp. 221-229. Grune & Stratton, New York.
31. Holm, L.-E. (1980): *Incidence of Malignant Thyroid Tumors in Man After Diagnostic and Therapeutic Doses of Iodine-131*. Doctoral Thesis, Stockholm.
32. Holm, L.-E., Lundell, G., and Walinder, G. (1980): Incidence of malignant thyroid tumors in humans after exposure to diagnostic doses of iodine-131. I. Retrospective cohort study. *J. Natl. Cancer Inst.*, 64:1055-1059.
33. James, R. A. (1964): *Estimate of Radiation Dose to Thyroids of the Rongelap Children Following the Bravo Event*. UCRL 12273.
34. Klassovskii, Iu. A. (1967): Dependency of irradiation effect on determination of dose in thyroid histological structures. In: *Sb. Mater. Radiatsionnaia Endokrinologiya*, edited by A. A. Voitkevich, pp. 40-42. Akad. Med. Nauk SSSR (Trans., NIH-71-99).
35. Klinck, G. H., and Winship, T. (1955): Occult sclerosing carcinoma of the thyroid. *Cancer*, 8:701-706.
36. Larsen, P. R. (1976): Radioimmunoassay of thyroxine, triiodothyronine, and thyrotropin in human serum. In: *Manual of Clinical Immunology*, edited by N. R. Rose and H. Friedman, pp. 222-230. American Society of Microbiology, Washington, D.C.
37. Larsen, P. R., Conard, R. A., Knudsen, K. D., Robbins, J., Wolff, J., Rall, J. E., Nicoloff, J. T., and Dobyns, B. M. (1982): Thyroid hypofunction after exposure to fallout from a hydrogen bomb explosion. *J.A.M.A.*, 247:1571-1575.
38. Lawrence, A. M., Wilber, J. F., and Hogan, T. C. (1973): The pituitary and primary hypothyroidism. *Arch. Intern. Med.*, 132:327.
39. Lessard, E. T., Miltenberger, R. P., Cohn, S. H., Musolino, S. V., and Conard, R. A. (1984): Protracted exposure to fallout: The Rongelap and Utirik experience. *Health Phys.* (in press).
40. Lindsay, S., and Chaikoff, I. L. (1964): The effects of irradiation on the thyroid gland with particular reference to the induction of thyroid neoplasms: A review. *Cancer Res.*, 24:1099-1107.
41. Maloof, F., Dobyns, B. M., and Vickery, A. L. (1952): The effects of various doses of radioactive iodine on the function and structure of the thyroid of the rat. *Endocrinology*, 50:612-638.
42. Marks, S., and Bustad, L. K. (1963): Thyroid neoplasms in sheep fed radioiodine. *J. Natl. Cancer Inst.*, 30:661-673.
43. Maxon, H. R., Saenger, E. L., Thomas, S. R., Buncher, R. C., Kereiakes, J. G., Shafer, M. L., and McLaughlin, C. A. (1980): Clinically important radiation-associated thyroid disease: A controlled study. *J.A.M.A.*, 244:1802-1807.
44. Meissner, W. A., and Warren, S. (1969): *Tumors of the Thyroid Gland*, Fascicle 4, Second Series, pp. 30-36. Armed Forces Institute of Pathology, Washington, D.C.
45. Modan, B., Ron, E., and Werner, A. (1977): Thyroid neoplasms in a population irradiated for scalp tinea in childhood. In: *Radiation-Associated Thyroid Carcinoma*, edited by L. J. DeGroot, L. A. Frohman, E. L. Kaplan, S. Refetoff, pp. 449-457. Grune & Stratton, New York.
46. National Council on Radiation Protection and Measurements (1975): *Protection of the Thyroid Gland in the Event of Releases of Radioiodine*, NCRP Report 55. NCRP, Washington, D.C.
47. Parker, L., Belsky, J. L., Yamamoto, T., Kawamoto, S., and Keehn, R. J. (1974): Thyroid carcinoma after exposure to atomic radiation. *Ann. Intern. Med.*, 80:600-604.
48. Pochin, E. E. (1972): Frequency of induction of malignancies in man by ionizing radiation. In: *Handbuch der Medizinischen Radiologie*, edited by O. Olsson et al., pp. 341-355. Springer-Verlag, Berlin.
49. Rallison, M. L., Dobyns, B. M., Keating, F., Jr., Rall, J. E., and Tyler, F. H. (1975): Thyroid nodularity in children. *J.A.M.A.*, 233:1069-1072.
50. Saenger, E. L., Silverman, F. N., Sterling, T. D., and Turner, N. E. (1960): Neoplasia following therapeutic irradiation for benign conditions in childhood. *Radiology*, 74:889-904.
51. Sampson, R. J. (1976): Thyroid carcinoma. *N. Engl. J. Med.*, 295:340.

52. Seyama, S., Ishimaru, T., Iijima, S., and Mori, K. (1979): Primary intracranial tumors among atom bomb survivors and controls, Hiroshima and Nagasaki, 1961-1975. Radiation Effects Research Foundation Technical Report 15-79, Hiroshima.
53. Spitalnik, P. F., and Straus, F. H. (1978): II. Patterns of human thyroid parenchymal reaction following low-dose childhood irradiation. *Cancer*, 41:1098-1105.
54. Sutow, W. W., and Conard, R. A. (1969): The effects of fallout radiation on Marshallese children. In: *Radiation Biology of the Fetal and Juvenile Mammal*, edited by M. R. Sikov and D. D. Mahlum, pp. 661-673. AEC Symposium Series No. 17 (CONF-690501). U.S. Atomic Energy Commission, Washington, D.C.
55. Sutow, W. W., Conard, R. A., and Thompson, K. H. (1982): Thyroid injury and effects on growth and development in Marshallese children accidentally exposed to radioactive fallout. *Cancer Bull.*, 34:90-96.
56. United Nations Scientific Committee on the Effects of Atomic Radiation (1977): *Sources and Effects of Ionizing Radiation. Annex G: Radiation Carcinogenesis in Man*, pp. 361-423. Publ. E.77.IX.1. United Nations, New York.
57. United States Nuclear Regulatory Commission, Reactor Safety Study (1977): *An Assessment of Accident Risks in U.S. Commercial Nuclear Power Plants. Appendix VI, Calculations of Reactor Accident Consequences. WASH 1400, NUREG-75/014. U.S. NRC, Washington, D.C.*
58. Vagenakis, A. G., Doole, K., and Braverman, L. E. (1976): Pituitary enlargement, pituitary failure, and primary hypothyroidism. *Ann. Intern. Med.*, 85:195-198.
59. Vasilenko, I. Ia., and Klassovskii, Iu. A. (1967): Remote consequences of thyroid irradiation with radioactive iodine isotopes. In: *Sb. Mater. Radiatsionnaia Endokrinologiya*, edited by A. A. Voitkevich, pp. 17-18. Akad. Med. Nauk SSSR (Trans., NIH-71-198).
60. Wood, J. W., Tamagaki, H., Neriishi, S., Sato, T., Shelfon, W. F., Archer, P. G., Hamilton, H. B., and Johnson, K. G. (1969): Thyroid carcinoma in atomic bomb survivors of Hiroshima and Nagasaki. *Am. J. Epidemiol.*, 89:4-14.
61. Woolner, L. B., Beahrs, O. H., Black, B. M., McConahey, W. M., and Keating, F. R., Jr. (1968): Thyroid carcinoma: General considerations and follow-up data on 1181 cases. In: *Thyroid Neoplasia*, edited by U. Young and D. R. Inman, pp. 51-77. Academic Press, New York.
62. Walinder, G., Jonsson, C.-J., and Sjoden, A.-M. (1972): Dose rate dependence in the goitrogen stimulated mouse thyroid. *Acta Radiol. Ther. Phys. Biol.*, 11:24-36.
63. Wall, I. B. (1982): New perspectives on the radiological consequences of a reactor accident. Presented at 9th Energy Technology Conf., Washington, D.C., February.