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LATE MEDICAL CONSEQUENCES OF EXPOSURE TO RADIOACTIVE FALLOUT

RONGELAP AND UTIRIK 35 YEARS AFTER "BRAVO"

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Data collected by the Brookhaven Medical Program on the late medical consequences of the exposure to radioactive fallout originated from the detonation of a thermonuclear device on Bikini atoll in Marshall Islands are discussed.

INTRODUCTION

March 1, 1990, will be the 36th anniversary of the detonation, from a tower on Bikini atoll in the Marshall Islands, of a thermonuclear device, BRAVO, which resulted in a serious fallout accident. The yield of the explosion was considerably greater than expected. This, plus unpredicted wind shifts in the upper atmosphere, caused the radioactive cloud to drift over and deposit fallout on several inhabited atolls to the east: Rongelap with 64 people, Ailingnae with 18 people, Rongerik with 28 American servicemen, and Utirik with 157 people. A Japanese fishing vessel, the Lucky Dragon, with 23 fishermen aboard was also exposed. The fallout began on Rongelap about four to six hours after detonation, on Rongerik at about seven hours, and on Utirik at about 22 hours. The duration of the fallout is estimated to have been about 12 hours, the greater part occurring early in the period. Within two days the exposed people were evacuated and taken to Kwajalein, 175 miles to the south, where decontamination commenced. A medical team arrived to examine and treat them for the anticipated radiation injury. The findings of the medical team, which included acute hematological and dermatological abnormalities, were subsequently published and are reviewed below (1). The Japanese fishermen received medical evaluation and follow-up, and these results were also published (2). The U.S. servicemen were returned to duty, but, despite attempts by the former director of the Marshall Islands medical program, focused periodic medical examinations for them were not provided by the military. The whole-body radiation doses in rem received by the different groups were as follows: Rongelap - 190; U.S. servicemen - 155; Ailingnae - 115; Utirik -

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people that had been residing temporarily on Ailingnae, were not able to reinhabit their home island for three years. During this period a program for long-term medical follow-up of the Marshallese was instituted.

FEATURES OF THE MEDICAL PROGRAM

The chronicling of the medical events involving the exposed Marshallese after 1954 has been one of the tasks of the Marshall Island's medical program. Humanitarian concern for the Marshallese and for other human populations that might suffer from some future exposure continues to be manifested by the interest of many individuals and institutions worldwide that request the program's published reports, a selection of which is included in the reference section (3-8).

The general health of the exposed population, morbidity directly or indirectly related to the exposure, and present and future risks continue to be monitored and reported by the Marshall Island's medical program. As part of its health care delivery, the program pursues two related objectives. One is the provision of a cancer-oriented annual examination that follows as nearly as is practicable, the recommendations of the American Cancer Society. The other is to place in perspective the risks of radiation exposure as they relate to the overall health of the individual and the community. Diabetes mellitus, for example, is a major health problem in the republic of the Marshall Islands, affecting some 20% of the adults examined by the medical program and causing renal failure, blindness, infection, peripheral neuropathy, impotence and accelerated atherosclerotic disease. The importance of diabetes, diseases of poor sanitation, and other serious health hazards should not be trivialized by excessive attention to radiation injury incurred almost two generations earlier. Nevertheless, the late morbidity from that irradiation can in no way be considered trivial. Indeed, it is the purpose of this presentation to show why that is so. But first it is appropriate to review the policies and procedures of the medical program in recent years.

Under congressional mandate, the U.S. Department of Energy has a contract with the Medical Department of Brookhaven National Laboratory to provide for the diagnosis and treatment of radiation-related disease among the exposed populations of Rongelap and Utirik. Although considerable effort is spent on the care of acute and chronic illnesses of any etiology, a program is in place which is oriented toward the problems posed by their 1954 radiation exposure. These people must be considered at increased risk for malignant disease, and chief among the responsibilities of an on-going program is a cancer-related evaluation which includes a review of systems and a complete medical examination, advice on decreasing risk factors for cancer and on self-detection of lesions, pelvic examinations with Papanicolaou smears, stool testing for occult blood, annual mammography (introduced when low dose techniques became available), and flexible

sigmoidoscopy every three years for those 50 years of age or older. In addition, since the radiation exposure of the Marshallese was of a unique type involving both external and internal exposures, a tabulation of risks derived from the statistics of other irradiated populations may not cover the range of late consequences that could befall them. Data collected by the Brookhaven Medical Program suggested other late effects of radiation exposure in man, effects which include an increase in incidence of pituitary neoplasms, hypothyroidism, thyroid nodularity, and a trend to lower blood cell counts. Therefore, the medical program has, for many years, included annual thyroid examinations by an endocrinologist or surgeon, thyroid function testing for all exposed persons, thyroid suppression with thyroid hormone for all the Rongelap-exposed population (the intent being to decrease the likelihood of thyroid nodules and cancer), annual blood counts, and evaluation for paraneoplastic and other evidence suggestive of neoplasia, such as hypogammaglobulinemia, monoclonal spikes on serum protein electrophoresis, hypercalcemia, and elevated alpha-fetoprotein levels in persons known to be seropositive for hepatitis B surface antigen. There is also ongoing evaluation for clinical evidence of depression in immunocompetence, for the exposed population may be at increased risk for unusual manifestations of infectious diseases.

Medical examinations and services are performed primarily aboard a vessel chartered by the U.S. Department of energy. The physicians for the medical team are volunteers selected from around the U.S., most being faculty members of well-known academic medical institutions. The participation of many excellent medical specialists has undoubtedly been a major factor in the acceptance of the Marshall Island's medical program by the population it serves, for the enrollment of the Marshallese is, of course, voluntary. The percent of persons in the exposed and unexposed groups who appear for the voluntary examination remains high. In 1987, of those available for examination, the acceptance rate was 95% for Rongelap, 90% for Utirik, and 72% for the unexposed population. Over a three-year period it was 97% for Rongelap, 100% for Utirik, and 94% for the unexposed. In addition, the acceptance rate for mammography among eligible women has been 100%. For sigmoidoscopy, about 50% of age-eligible persons elect to undergo this procedure.

It is important to understand that the Marshall Island's medical program is distinct from the Marshallese Government Health Services which is a national program of health care which encompasses two hospitals and a network of clinics scattered over some 20 atolls. This network serves the entire population of the Marshall Islands, which numbers about 40,000, whereas the U.S.-funded medical program is directed at those persons, now numbering 160, who were exposed to fallout radiation in 1954. However, the program also provides equivalent health care for all persons residing on Rongelap and Utirik atolls at the time of medical team visits, regardless of their radiation history.

LATE MEDICAL FINDINGS

Thirty-six years of observation continue to show no detectable increase in mortality in the exposed population (Figure 1). The survival curves of the Rongelap population, which received a whole body radiation dose of 190 rad, the Utirik population which received 11 rad, and an

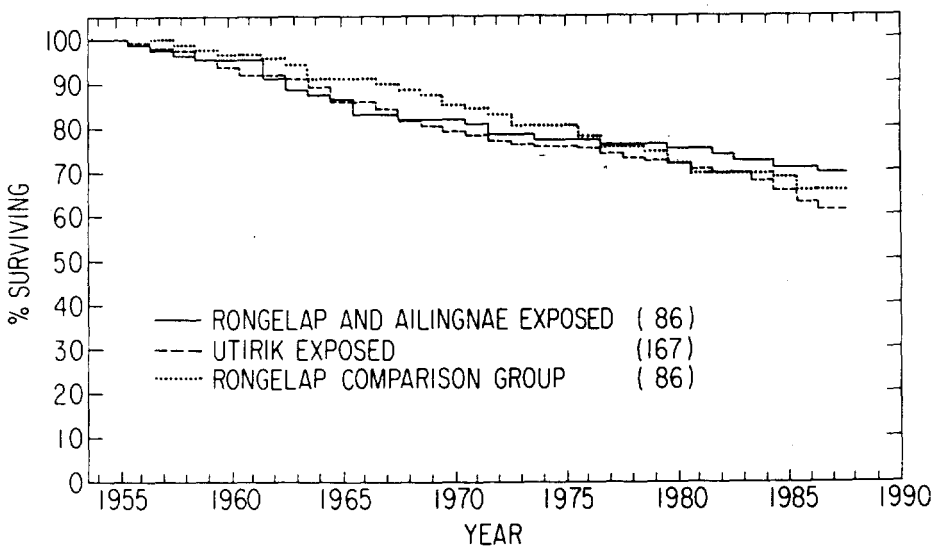

Figure 1. Percent survivors of the different exposure groups since 1954. The number of persons in each group is given in parentheses.

unexposed group of Rongelap people selected in 1957 and matched approximately by age and sex to the exposed Rongelap group continue to be similar. This is not surprising because Japanese A-bomb survivors, which included a far greater number of radiation-exposed individuals, many of whom received a much higher radiation dose than the people of Rongelap, have also had no overall shortening of life-span, even when correlated with radiation dose (9). In addition, a separate study of Nagasaki A-bomb survivors revealed their 1970-1984 age-specific death rates from all causes to be lower than controls, although it has been suggested that the effectiveness of programs providing health screening for that population might have led to an underestimation of the effect of radiation on mortality (10). Clearly, therefore, concern over the consequences of the 1954 exposure transcends mortality statistics.

Miscarriages

It is not known if there was an increase in the rate of miscarriage of conceptions following fallout exposure. Although medical program data were interpreted as showing an increase in adverse pregnancy outcomes during the first five years, it is now known that normally up to 40% of all conceptions abort, usually in the first few weeks of pregnancy. Techniques to determine this rate were not available in the 1950s. Therefore, all that can be said about miscarriages in those early years is that, whereas the birthrate in the Marshall Islands in 1957 was 37.3 per 1000 population, that of the Rongelap population, averaged over a six-year period, was 48 per 1000 per year.

Growth and Development

The exposed children were followed closely for evidence of developmental delay. Stature, weight, and osseous maturation were assessed over many years. Growth studies on young people exposed to radiation from atomic bombs in Hiroshima and Nagasaki showed that their adult heights were significantly lower than those of unexposed children. It was determined that there was no significant difference in mean adult stature between those who were exposed on Rongelap and Ailingnae and those who were not. Nevertheless, two young boys clearly had retarded growth (11). It was subsequently determined that this was due to hypothyroidism. When thyroid replacement was instituted, their growth accelerated, thus confirming that this abnormality was secondary to radiation-induced thyroid damage rather than to some other less well-defined effect of radiation.

Chromosomal and Genetic Effects

In 1964 chromosome preparations were obtained from lymphocytes cultured from the peripheral blood of many of the exposed population (12). When compared to an unexposed group, an increase in chromosomal aberrations attributable to radiation were detected in the Rongelap population. There is little of clinical significance in this finding, for radiation-induced chromosomal abnormalities in man have not been associated with any disease state. On the other hand, they are known to be useful as a dosimeter. However, in the situation which prevailed on Rongelap, much more accurate estimates of dose were obtained using direct readings near the time of the exposure.

No increase in birth defects has been found in the years following the exposure. This is not surprising in light of the evidence from the follow-up of Japanese A-bomb survivors; Radiation Effects Research Foundation workers, using eight parameters, were unable to detect a statistically significant increase in genetic abnormalities in the exposed population despite its large size and the great range of radiation doses received (13); i.e., a genetic effect of radiation on man has yet to be demonstrated, even though studies of experimental animals and microorganisms have clearly shown such an effect.

Aging

To determine if the exposed population was suffering accelerated aging, a series of tests were performed which evaluated the skin, visual and auditory function, strength, blood pressure, and numerous other parameters (14). It was concluded that there was no evidence of premature aging.

Hematology

In 1972 acute leukemia was diagnosed in a young man who was an infant at the time of the 1954 exposure (15). It was calculated that the leukemia was likely due to that irradiation. No further hematologic malignancies have been diagnoses in the exposed population since that time. There has been a tendency for the exposed Rongelap population to have, on the average, lower neutrophil, lymphocyte and platelet counts than the comparison population (Figure 2), but no

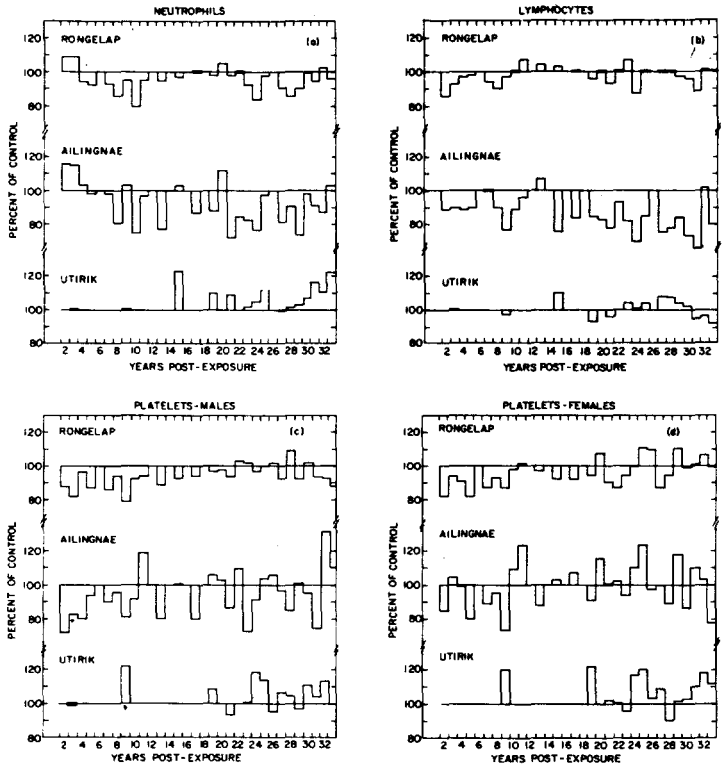

Figure 2. Annual mean white blood cell counts and platelet counts of the different exposure groups (age five years or more) expressed as percent of control, beginning two years after exposure. Annual blood cell counts did not begin on Utirik until 1973.

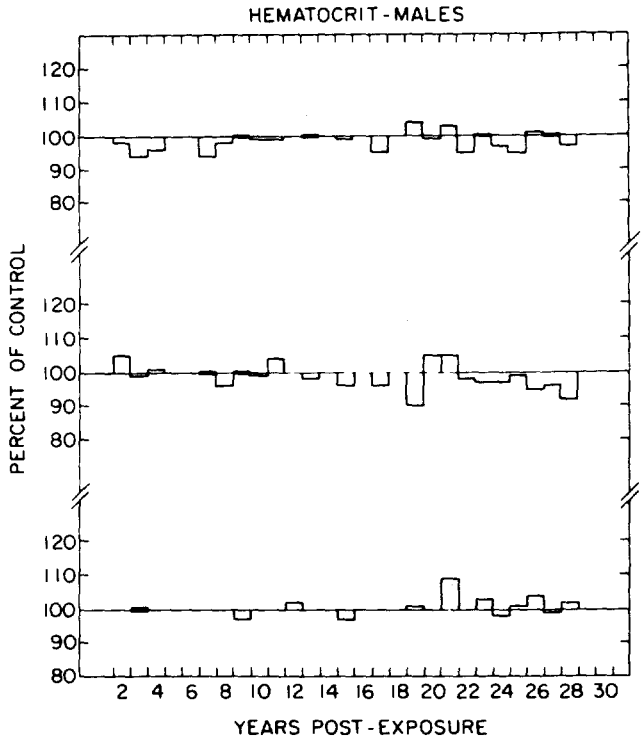

Figure 3. The mean hematocrit, a measure of the degree of anemia in a community, has shown no significant variation from control values. Top - Rongelap; middle - Ailingnae; bottom - Utirik.

individuals have had a clinically significant depression of any cell type (8). Hemoglobin/hematrocrit levels have been virtually identical to the unexposed (Figure 3).

Immunologic Status

In 1957 the first of several tests for evaluating the immune function of exposed Marshallese was performed (16). The serologic responses to primary and secondary challenges of tetanus toxoid were found not to be significantly different between exposed and unexposed persons, although the range of titers was great, the number of persons tested was small, and the primary response was somewhat lower in the exposed. In 1959 complement fixation tests for a battery of viral and rickettsial disease (including influenza, mumps, and adenovirus) were performed. The Rongelap group had lower mean titers than the comparison group for most antibodies tested. No significant

differences were noted in serum protein electrophoretic studies in 1957, 1974, or 1982. Lymphocyte counts were significantly lower in the exposed Rongelap population in 1985, but in most years this was not found.

Ophthalmologic Examinations

In 1981 ophthalmologic examinations revealed the presence in several individuals of lesions compatible with ocular toxoplasmosis. Toxoplasma gondii is an intracellular protozoan which is most commonly disseminated among humans via cat feces or inadequately cooked pork. It elicits both humoral and cellular immune responses, and medical complications are more severe in those individuals with a suppressed immune mechanism. Because of the potential risk of toxoplasmosis to exposed persons, a serologic survey for Toxoplasma antibodies was performed in 1982 (Table 1) (17). It was determined that nearly 100% of the Marshallese population had been infected with Toxoplasma, a finding to be expected on the basis of investigations by others in tropical regions. However, neither antibody titers nor ocular examination provided evidence that the exposed population was at unusual risk for toxoplasmosis or its complications.

Another ubiquitous and serious infection, particularly in tropical areas, is viral hepatitis, including hepatitis B. This disease was also evaluated by a serologic survey (Table 2) (18). Again, nearly 100% of Marshallese examined had evidence of past exposure to hepatitis B. However, neither antibody titers or the presence of hepatitis B surface antigen suggested an increase in risk of hepatitis B complications among the Rongelap exposed population when compared with the unexposed.

Another clinical marker of immune competence is the ability to respond to skin test challenge with several antigens. Therefore, a survey of skin test responsiveness to Mycobacterium tuberculosis and Candida was undertaken (Table 3). No evidence was found to indicate inadequacy of the delayed hypersensitivity response among the Rongelap population.

There has been no evidence to date of autoimmune disorders. Rheumatoid arthritis has yet to be diagnosed with certainty, and a survey for rheumatoid factor uncovered only one positive titer, a prevalence of 0.4% compared to 4-40% reported for various age groups in the U.S. The relative scarcity of diseases of purported autoimmune etiology extends to thyroid disease as well. Radiation-induced thyroid hypofunction, diagnosed in several exposed Rongelap individuals, was not found to be increased among Japanese A-bomb survivors. This difference reflects the larger radiation dose absorbed by thyroids of the Marshallese, a consequence of ingestion of radioiodines. The question arises as to whether thyroid hypofunction might also reflect some immunologic damage to the thyroid. That damage is mediated, in part, by circulating autoantibodies that are apparently cytotoxic. Antimicrosomal antibodies are important in the diagnosis of autoimmune thyroiditis, a disease process commonly progressing to hypothyroidism. Antithyroglobulin

Table 1

Serum toxoplasma titers and chorioretinal scars.

A) EXPOSURE GROUP

	Rongelap and Ailingnae	Utirik	Comparison
MLT*	6.66±3.72	8.29±2.49	7.81±2.49
	(61)**	(97)	(100)
%<4	18.0%	3.1%	4.0%
MLT minus <4	8.12±2.19	8.55±2.03	8.14±1.95

B) ISLAND OF RESIDENCE

	Ebeye	Majuro	Rongelap	Utirik
MLT	7.69±2.51	8.11±3.34	7.22±3.23	8.48±2.56
	(103)	(62)	(87)	(172)
MLT minus	7.84±2.44	8.57±2.64	7.62±2.84	8.49±2.36
Rongelap and	(69)	(53)	(71)	(172)
Ailingnae				
Exposed				

C) AGE DISTRIBUTION

	<10 YR	10-19 YR	>19 YR
Rongelap and	5.89±3.55	8.27±3.58	6.82±3.88
Ailingnae	(28)	(11)	(22)
Utirik	8.36±3.00	7.86±1.83	8.36±1.82
	(50)	(14)	(33)
Comparison	7.49±2.56	7.76±2.80	8.15±2.26
	(39)	(21)	(40)

D) RETINAL LESIONS

	Rongelap and Ailingnae	Utirik	Comparison
	(51)	(98)	(86)
Number	2	1	2
%	3.9	1.0	2.3

* MLT = mean log titer.

** Number of persons tested is given in parentheses.

Table 2

Summary of Positive Serologic Tests for Hepatitis B Surface Antigen (HBsAg), Antibody to Surface Antigen and Antibody to Core Antigen Among 314 Marshallese

	NUMBER TESTED	ONE OR MORE POSITIVE TESTS		HBSAG POSITIVE	
By sex					
Male	134	123	(91.8)*	20	(14.9)
Female	180	165	(91.7)	16	(8.9)
Combined	314	288	(91.7)	36	(11.5)
By age (yr)					
<29	46	43	(93.5)	3	(6.5)
29-49	175	158	(90.3)	20	(11.4)
>49	93	87	(93.3)	13	(14.0)
By atoll of residence**					
Kwajalein	100	89	(89.0)	10	(10.0)
Majuro	74	68	(91.9)	4	(5.4)
Rongelap	61	58	(95.1)	3	(8.5)
Utirik	76	70	(92.1)	19	(25.0)
By radiation exposure group					
Rongelap exposed	61	50	(82.0)	2	(3.3)
Utirik exposed	112	103	(92.0)	21	(18.8)
Ronglap comparison	95	86	(90.5)	10	(10.5)
By atoll of residence, excluding Rongelap exposed					
Ebeye	69	63	(91.3)	6	(8.7)
Majuro	61	58	(95.1)	4	(6.6)
Rongelap	44	42	(95.5)	3	(6.8)
Utirik	76	70	(92.1)	19	(25.0)

* Percent of the total population tested is shown in parentheses.

** Three persons resided outside the atolls listed.

Comparison
7.81±2.49
(100)
4.0%
8.14±1.95

Utirik
8.48±2.56
(172)
8.49±2.36
(172)

≥19 YR
6.82±3.88
(22)
8.36±1.82
(33)
8.15±2.26
(40)

Comparison
(86)
2
2.3

Table 3

Skin test responsiveness by radiation exposure group*

Radiation Category	No. in Each Category	No. Tested	Tuberculin Negative	Candida Negative
Rongelap	62	38	16 (42.1%)	2 (5.3%)**
Utirik	137	72	39 (54.2%)	0 (0.0%)
Comparison	135	68	35 (51.5%)	2 (2.9%)

* See text for definition of positive and negative tests.

** Two persons, an 83-year-old Rongelap exposed man and a 43-year-old unexposed woman, had positive tuberculin tests despite negative reactions to Candida antigen.

Table 4

Antithyroid antibodies in the different radiation exposure groups

Exposure group (n)	Elevated antithyroglobulin	Percent elevated
Rongelap (55)	2	4%
Utirik (94)	4	4%
Comparison (82)	2**	2%

* The levels ranged between 6 and 11 U/1, with normal levels being ≤ 5 U/1.

** One subject had elevated antimicrosomal antibodies (35 U/1) and a history of Grave's disease with hyperthyroidism.

antibodies are less specific indicators of thyroid autoimmune disease, but are useful as a screening test. These two antibodies were sought in Marshallese sera. The results indicated no significant difference among the exposure groups (Table 4). It is notable that in one U.S. study prevalence of antithyroglobulin antibodies was 4.8% in normal children, and that prevalence increases with age. These data indicate that autoimmune thyroid disease is not common in the Marshallese, regardless

of a history of radiation exposure. The lack of evidence for an association of autoimmune disease with radiation exposure is consistent with data obtained by the Radiation Effects Research foundation in Japan.

In summary, at this point there is no evidence that the 1954 exposure has significantly affected the immune status of the Marshallese or placed the exposed population at increased risk for infection. However, the absence of such evidence on a group basis, attention to this possible risk will continue.

Thyroid Neoplasms

The most obvious effect of radiation injury on the exposed Marshallese has been thyroid disease. Both overt and subclinical hypothyroidism have been identified; these events are referred to elsewhere in this presentation. The other major thyroid abnormality has been nodule formation. The reason for the predominance of thyroid disease in this population is that the radiation dose to the thyroid was much greater than the whole body dose. That discrepancy was the consequence of ingestion of radioisotopes of iodine prior to removal of the people from the contaminated atolls in March, 1954. The estimate of thyroid radiation dose has been recently revised (19), and a summary of age-specific doses on Rongelap and Utirik is shown in Table 5.

Since 1963, when the first of the series of thyroid nodules was detected in the exposed population at the time of the annual Brookhaven examinations, thyroid surgery has been necessary to determine whether thyroid cancer was present. The specific diagnoses, as determined by an

Table 5
Revised thyroid internal dose estimates*
Rongelap and Utirik

	Rongelap	Utirik
Adult Male	1000 rad	150
Adult female	1100	160
9-year-old	2000	300
1-year-old	5000	1400
Newborn	250	48

*From reference (19).

expert panel of pathologists, are listed in Table 6. Not included is a benign nodule diagnosis in 1989 in a Utirik man. Most benign nodules and all the thyroid carcinomas have occurred in females. "Adenomatous nodules" are included in the tabulation even though it is highly debatable that they are true neoplasms. "Occult papillary carcinomas," also tabulated, are, with rare exceptions, harmless tumors. A recently reported autopsy series from Germany indicated occult papillary thyroid carcinomas were present in 6.2% of cases. Since there was no predilection for age it was concluded, as in earlier studies, that occult papillary carcinomas have no propensity to cause clinically apparent thyroid disease. However, there is some evidence that the occurrence of these small tumors may be increased following radiation exposure.

No mortality has been attributable to thyroid cancer in the exposed Marshallese. Most thyroid cancers, including those that are radiation-induced, are of the papillary variety. The mortality of

Table 6

Thyroid nodules diagnosed at surgery through 1989

	Adenomatous nodules	Adenomas	Papillary cancers	Follicular cancers	Occult cancers
Rongelap (67)*	17	2	5	-	1
Ailingnae (19)*	4	-	-	-	1
Utirik (167)*	12	4	4	1***	6
Comparison (227)**	4	1	2	-	2****

Not Included are the following unoperated (and therefore unconfirmed) nodules:
Rongelap - 1; Ailingnae - 1; Utirik - 1; Comparison - 5.

Included are all consensus diagnoses of a panel of consultant pathologists, two different lesions were detected in one person form Rongelap, one form Ailingnae, and 3 from Utirik.

* Number of persons (including those in utero) who were originally exposed.

** This number includes all persons who have been in the Comparison group since 1957. Some have not been seen for many years; others were added as recently as 1976.

*** Equally divided opinion in one case, follicular carcinoma vs. atypical adenoma

**** Majority opinion in one case; occult papillary carcinoma vs. follicular carcinoma. The same patient had lymphocytic thyroiditis.

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Follicular cancers	Occult cancers
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-	1
1***	6
-	2****

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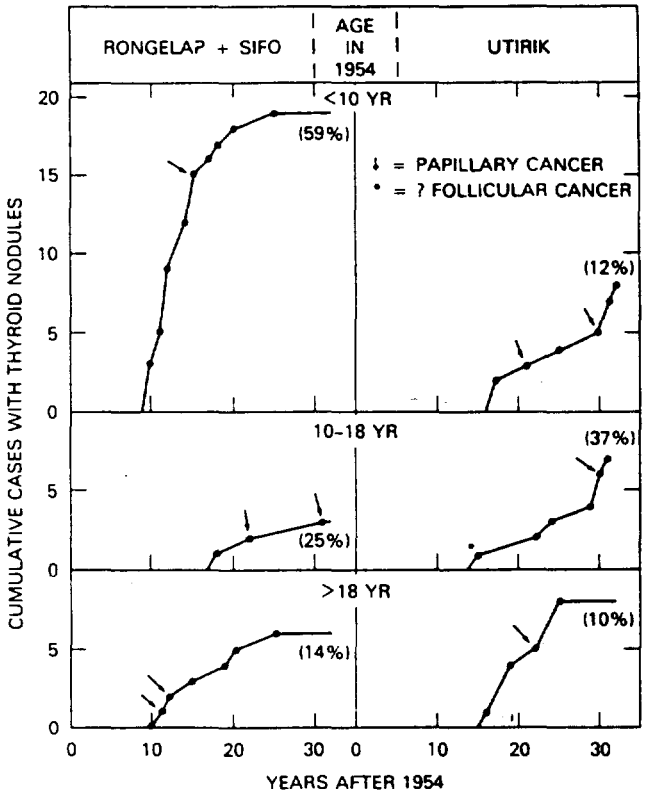


Figure 4. The accrual of cases with thyroid nodules and thyroid cancer in the exposed Rongelap population as a function of age at the time of exposure in 1954. The <10 year-old group includes those exposed in utero.

treated papillary thyroid cancer is relatively low, about 4%, with those persons less than 40 years of age at the time of diagnosis having a better prognosis.

The cumulative experience of benign plus malignant nodule development as a function of age at exposure shows clearly the increased susceptibility of the younger population to nodule induction (Figure 4). It was noted that the ratio of thyroid carcinomas to benign nodules was .15, somewhat lower than the ratio of .30 reported following medical x-ray therapy (20).

It appears that there is an inverse correlation between the radiation dose absorbed by the thyroid and the time after exposure for development of the benign adenomatous nodules (Figure 5). However, since the thyroid-absorbed radiation dose was determined primarily by age at exposure

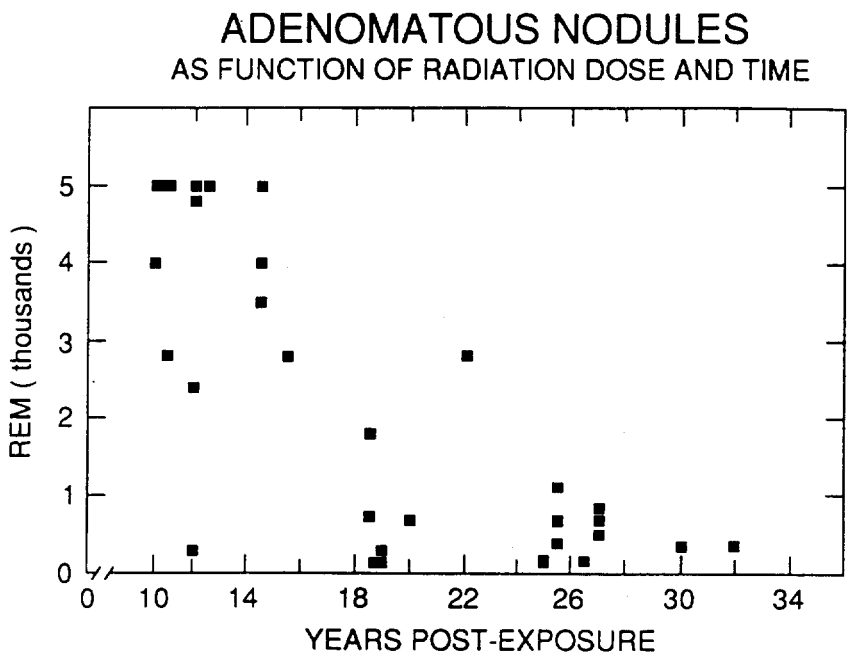
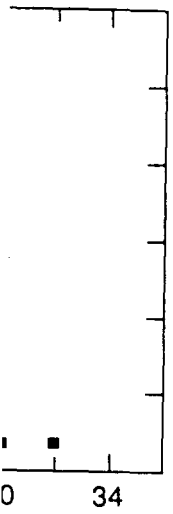


Figure 5. The time required to develop adenomatous nodules of the thyroid following radiation exposure appears, in this graph, to be dose-related. However, the thyroid-absorbed radiation dose was highly dependent on the age at exposure.

(children receiving greater doses than adults), another interpretation of Figure 5 is that the time for development of adenomatous nodules following radiation exposure varies directly with age at exposure.

Nonthyroidal Cancers

There are several points that are relevant for those who would apply an epidemiologic analysis to cancer deaths among the exposed Marshallese. First, since the Marshall Islands medical program has not maintained a year-round medical presence on the different atolls where the exposed population may be found, causes of death are obtained from records and verbal accounts of health aides and family members living on those atolls, and from records and death certificates at the Marshallese hospitals. Autopsies are seldom performed. Therefore, available information on cancer deaths may be either inaccurate or incomplete (or both). Second, in areas where health care is limited there is often increased mortality from nonmalignant disease, and an increase in cancer



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incidence has been viewed as evidence of improved overall health of some populations because it reflects improvements in longevity. Third, in attempting to determine whether there has been an increase in cancer deaths in the exposed Marshallese it should be noted that from 1950-1985 there had been 5936 cancer deaths among 75,991 A-bomb survivors. Three hundred and forty of these (6% of the total cancer deaths) are thought to be attributable to the 1945 radiation exposure (21).

Table 7
Fatal cancers, exposed and unexposed groups

Rongelap/Utirik	Comparison
Ovary	Hepatoma (?)
Cervix (?)	Leukemia, acute
Uterus (?)	Cervix (?)
Leukemia, acute	Breast
Stomach	Lymphoma (?)
Hepatoma	Lung
Breast	Colon (?)
Central nervous system	Central nervous system
Lung	

(?) = Diagnosis not confirmed

The small number of the exposed Marshallese, the smaller number of cancer deaths, and the naturally occurring fluctuations in cancer incidence will make statistical detection of any excess cancer mortality impossible in this population.

Five of 26 deaths among the 86 persons in the exposed Rongelap population have been recorded as due to cancer. If these diagnoses are correct, then 19% of total mortality over 36 years has been due to cancer. In comparison, cancer accounts for 22% of total mortality in the U.S. In the unexposed Marshallese group examined by the medical program, eight of 63 known deaths (13%) may have been due to malignant disease. The types of lethal cancers which have been diagnosed are given in Table 7. It is pertinent that the most frequently lethal cancers in the U.S. are lung, breast, colon and leukemia/lymphoma. The frequency of different cancers induced by whole-

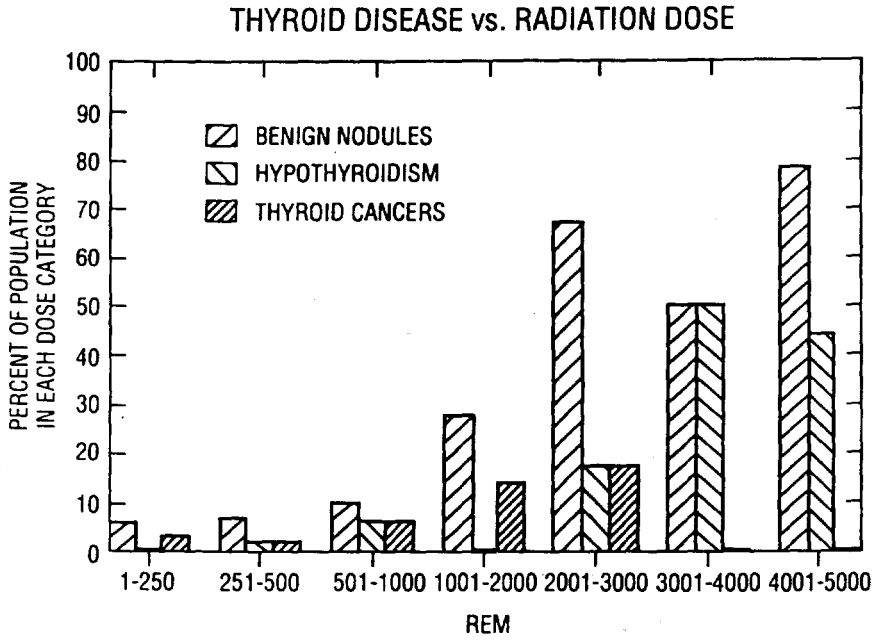

Figure 6. Thyroid-absorbed radiation dose and subsequent development of benign thyroid nodules, thyroid carcinomas, and hypofunction.

population, both benign nodules and thyroid hypofunction display a similar correlation with radiation (Figure 6), and in contrast to thyroid cancer, adenomatous nodules have been very common (Table 6). Adenomatous nodules are rarely of clinical significance, because they do not evolve into cancers. Surgery is necessary only to exclude the latter diagnosis. Nevertheless, the clinical evaluation required to establish a diagnosis is associated with its own morbidity. Prominent in this morbidity is thyroid surgery itself, a procedure that requires general anesthesia and results in a cosmetic defect and the unavoidable removal of some normal thyroid tissue.

Thyroid Hypofunction, Radiation-Induced

Overt hypothyroidism was diagnosed in two Rongelap boys who were infants at the time of exposure (11). In addition, subclinical hypothyroidism unrelated to thyroid surgery was confirmed in twelve other Rongelap persons (22). In 1987, a Utirik man was diagnosed as biochemically hypothyroid. He was two years of age at the time of exposure, and he is the first exposed person from Utirik to have this diagnosis.

body radiation is now thought by many to reflect the frequency of the different types of cancer normally occurring in a population. There is no known marker for radiation-induced cancer.

Noncancerous Thyroid Morbidity

The late somatic effects of exposure to ionizing radiation have been equated with cancer induction, the ultimate measure of those effects being expressed in mortality. Since cancer mortality from radiation exposure is low when compared to naturally occurring cancer mortality, it is not surprising that there is no observed increase in mortality among the radiation-exposed Marshallese. Nevertheless, much attention has been addressed to their cancer risk. On the other hand, limited attention has been given to morbidity from nonmalignant disease, principally of the thyroid, as a late consequence of radiation exposure, and yet these lesions have been of great clinical importance (Table 8).

Table 8
Late thyroid morbidity unrelated to diagnosis and treatment of thyroid cancer in 253 radiation-exposed Marshallese

Morbid event	Number of cases
Thyroid surgery for benign lesions	44
Hypothyroidism, radiogenic	15
Hypothyroidism, postsurgical	21
Hypoparathyroidism, postsurgical	2
Recurrent laryngeal nerve palsy	1
Pituitary tumor*	2
Total morbid events	84

Thyroid Surgery

Thirty percent of the Rongelap group and 11% of the Utirik group have had surgery for thyroid nodules that were ultimately found to be benign. The types of thyroid nodules found in the exposed population since 1963 can be grouped into cancers, adenomas, and adenomatous nodules. Cancers and adenomas are neoplasms. Adenomatous nodules, like adenomas, are benign, and are not properly categorized as neoplasms. Histologically, they are hyperplastic lesions. In the exposed

Hypothyroidism, Postsurgical

Despite efforts to mitigate loss of thyroid tissue, however, there continues to be evidence of an inordinantly high frequency of postsurgical thyroid hypofunction among the exposed population. Table 9 shows data obtained through 1987 illustrating this point. An increase in frequency of

Table 9
Marshallese with previously normal TSH levels who have developed elevated levels following thyroid surgery

Exposure group	Adult thyroid dose (rad)*	Number with surgery	Number with hypothyroidism**	Percent
Rongelap***	1200	23	14	61
Utirik	160	25	7	28
Comparison	None	11	1	8

* Average estimated dose for an adult male

** Biochemical evidence of thyroid hypofunction as indicated by at least two determinations of thyroid stimulating hormone $\geq$ 7.0 uU/1. Normal values are less than 6.0 uU/1.

*** Routine thyroxin suppression prescribed.

postsurgical thyroid hypofunction with increase in thyroid radiation dose is apparent, even though all thyroid surgery patients were advised to take thyroxin. However, the data in Table 9 must represent a minimum estimate of the prevalence of postsurgical thyroid hypofunction, for thyroxin was not purposely discontinued before testing. Some persons may have maintained normal serum levels of thyroid hormone after surgery only because they are adhering satisfactorily to the prescribed thyroxin regimen. In conclusion, these data reveal an inordinantly high frequency of postsurgical thyroid hypofunction in exposed persons who had normal thyroid function prior to surgery. Therefore, there appears to be significantly diminished thyroid reserve in many exposed persons, and although this diminution is not apparent from routine testing of hormone levels, it frequently can be clinically unmasked by thyroid surgery.

Postsurgical Hypoparathyroidism

Two women who had thyroid surgery for benign nodules developed clinically significant low calcium levels due to parathyroid gland injury at the time of surgery.

Laryngeal Nerve Injury

One Rongelap man developed this complication of thyroid surgery.

Pituitary Tumor Formation

Two women exposed as young children have developed pituitary tumors. These tumors are usually benign, causing disease in part because of their expansion inside a rigid structure (the skull). There is no known direct association between radiation exposure and development of a pituitary tumor, but there are reasons to suspect that pituitary tumor formation may be a late consequence of thyroid injury (23).

In summary, hypothyroidism and subclinical thyroid hypofunction, benign thyroid nodule formation, thyroid surgery with its attendant risks and complications, an excessive prevalence of thyroid hypofunction after thyroid surgery, and possibly pituitary tumors can be considered adverse delayed consequences of radiation injury in the exposed Marshallese. The tally comes to 85 morbid events in 253 persons. In contrast, the only evidence for what might be described as a "stochastic" effect of radiation exposure has been an increase in thyroid cancers in the Rongelap population, none of whom yet have evidence of residual disease. While several nonthyroidal cancers known to be inducible in humans by ionizing radiation have been documented in the exposed population, similar cancers have occurred in the unexposed population. Therefore, one may conclude that in the Marshallese experience the delayed expression of morbidity from nonmalignant disease caused by radiation has indeed been great and far exceeds that of malignant disease. This is an important point, for much of the morbidity has occurred despite our best attempts at prevention. In addition, a death made premature as a consequence of nonmalignant morbidity is not likely to be listed as radiation-related, for its detrimental effects are subtle and blend easily into the spectrum of human illness. Finally, a given malignant disease may be uncommon, but frequently fatal. Whereas nonmalignant radiation-related morbidity, while uncommonly lethal, may be highly significant by virtue of the large population that can be affected. To conclude, the sequence of thyroid-related morbidity provides a warning that biological misadventure does not occur in a vacuum.

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